Defining the clinical usefulness of vertebral fracture assessment

Lisa Johansson

Department of Internal Medicine
and Clinical Nutrition,
Institute of Medicine at
Sahlgrenska Academy
University of Gothenburg

Gothenburg, Sweden, 2022

UNIVERSITY OF
GOTHENBURG

Cover illustration by Lisa Johansson
Cover layout: Sahlgrenska Academy, communications department

Illustrations: Pontus Andersson (Pontus Art Production AB)

Defining the clinical usefulness
of vertebral fracture assessment

lisa.s.johansson@vgregion.se

ISBN 978-91-8009-568-6 (printed)
ISBN 978-91-8009-569-3 (epub)
http://hdl.handle.net/2077/70950
Printed in Borås, Sweden 2022
Printed by Stema Specialtryck AB

To Petter
Linnea & Emil

“Förverkliga något som Du alltid har drömt om,
och Du får uppleva något som Du aldrig drömt om!”

“Do something that you have always dreamt of,
and you will experience something that you have never dreamt of”

“Värp först och kackla sen!”

“Lay first and cackle later!”

Birgit Nilsson

Abstract

Objective: Vertebral fractures (VFs) are the most common osteoporotic fracture and among the strongest predictors for future fracture. VFs can be identified by vertebral fracture assessment (VFA) from lateral spine imaging (LSI) by dual-energy X-ray absorptiometry (DXA).

Aims: The overall aim of this thesis was to evaluate the clinical usefulness of VFA. More specifically, the different aims were to investigate associations between prevalent VFA-identified VFs with bone microstructure and bone strength, and also health-related quality of life (HRQL) and physical function. Further aims were to investigate whether or not VFA-identified VFs, according to their number and severity, predict incident fractures, and more specifically whether or not mild VFs (grade 1; 20% to 25% compression) increase fracture risk. The final aim was to determine whether VFA-identified VFs can improve fracture risk prediction beyond the clinical risk factors (CRFs) and femoral neck (FN) bone mineral density (BMD) used in the Fracture Risk Assessment Tool (FRAX).

Methods: The studies are based on the **S**ahlgrenska **U**niversity Hospital **P**rospective **E**valuation of **R**isk of **B**one Fractures (SUPERB), a population-based study of 3,028 older women aged 75-80 from Gothenburg. At baseline, BMD was measured by DXA, bone microstructure by high-resolution peripheral quantitative computed tomography (HRpQCT), cortical bone strength by microindentation, HRQL by self-administered questionnaires (SF-12), physical function by One Leg Standing (OLS), Timed Up and Go (TUG), walking speed, 30-second chair stand test and maximum grip strength. VFs were identified by VFA using DXA. Incident fractures were x-ray- verified or captured by diagnosis codes from the National Patient Register (NPR).

Results: Trabecular bone microstructure and bone geometry were impaired in women with VFs, but not independently of total hip (TH) BMD. Cortical porosity and cortical bone material strength were not associated with VFs. Physical health and physical function were worse in women with VFs compared with women without. In Paper

III, 213 women out of 2,095 women included, sustained a major osteoporotic fracture (MOF) during a median follow-up of 3.6 years. Women with only mild VF had increased risk for MOF independently of CRFs and FN BMD, compared with women without VF. In Paper IV, 422 women out of 2,852 women included, sustained a MOF during a median follow-up of 5.15 years. Independently of CRFs and FN BMD, VFA-identified VFs were associated with an increased risk of MOF, also according to number and severity of baseline VFs. VFA-identified VFs had a substantial impact on the 10-year probability of MOF (uplifting the 10-year probabilities by 1.19 to 1.40, depending on BMD) independently of self-reported prior fracture and other CRFs and FN BMD in FRAX.

Conclusions: VFA-identified VFs were associated with inferior trabecular bone volume fraction, TH BMD, worse physical health and physical function in older women. Mild VFs were independently associated with incident MOF, and VFA-identified VFs increase the 10-year probability of MOF substantially. Thus VFA is a clinically useful method for diagnosing relevant VFs and improves fracture prediction in older women.

Keywords: Vertebral fracture, vertebral fracture assessment, osteoporosis, DXA, HRpQCT, bone microindentation, mild vertebral fracture, physical function, fracture risk, incident fracture, older women.

Sammanfattning på svenska

Bakgrund: Kotkompression är den vanligaste osteoporosfrakturen och är en av de frakturer som starkast kan förutsäga en framtida icke-vertebral eller vertebral fraktur. Kotkompressioner kan diagnostiseras med ”vertebral fracture assessment” (VFA) från sidobild på ryggraden som kan göras i samband med bentäthetsmätning.

Syfte: Det övergripande syftet med avhandlingen var att undersöka den kliniska nyttan med VFA. Mer specifikt så var de olika frågeställningarna att undersöka om förekomst av kotkompression (diagnostiserade med VFA) var associerade med benegenskaper såsom benets mikrostruktur och styrka, men också undersöka associationer med hälsorelaterad livskvalité och fysisk funktion. Ytterligare frågeställningar var att undersöka om VFA kotkompressioner, beroende på antal och svårighetsgrad, förutsäger framtida frakturer, och mer specifikt om milda kotkompressioner (grad 1; 20% till 25% höjdreduktion) ökar risken för fraktur. Det undersöktes också om VFA kotkompressioner kan förbättra frakturrisk-bedömningen utöver den riskbedömning man kan få med hjälp av kliniska riskfaktorer och bentäthet från lårbenshals som används i det web-baserade frakturrisk verktyget FRAX (Fracture Risk Assessment Tool).

Metoder: Studierna i avhandlingen är baserade på Sahlgrenska Universitetssjukhus Prospektiva Estimering av Risk för Benfrakturer – SUPERB-studien, en populations-baserad studie som utgörs av 3028 äldre kvinnor från Göteborg. I samband med inklusion mättes bentäthet med dubbelfoton röntgenabsorbtiometri (DXA), benets mikrostruktur med högupplöst datortomografi, benets styrka med mikroindentering, hälsorelaterad livskvalité med självadministrerade frågeformulär (SF-12), fysisk funktion med enbensstående, TUG (Timed Up and Go), gånghastighet, uppresande från stol under 30 s och greppstyrka. Kotkompressioner diagnostiserades med VFA. Incidenta frakturer verifierades från röntgenbilder och röntgenutlåtande samt via diagnoskoder från Patientregistret från Socialstyrelsen.

Resultat: Trabekulär benmikrostruktur och bengeometri var nedsatt hos kvinnor med kotkompression, men inte oberoende av bentäthet från totalhöft. Kortikal porositet och kortikal benstyrka var inte associerat med förekomst av kotkompression. Fysisk hälsa och fysisk funktion var sämre hos kvinnor med kotkompression jämfört med kvinnor utan kotkompression. I delarbete III under en uppföljningstid på 3.6 år fick 213 kvinnor en större osteoporosfraktur (major osteoporotic fracture; MOF). Kvinnor med enbart milda kotkompressioner hade ökad risk för MOF oberoende av kliniska riskfaktorer och bentäthet i lårbenshals jämfört med kvinnor utan kotkompression. I delarbete IV under en uppföljningtid på 5.15 år fick 422 kvinnor en MOF. Kotkompressioner diagnostiserade med VFA var associerade med ökad risk för MOF, oberoende av kliniska riskfaktorer och bentäthet, och risken ökade med antal och svårighetsgrad på de prevalenta kotkompressionerna. Kotkompressioner diagnostiserade med VFA hade en väsentlig påverkan på 10-års sannolikheten för MOF i FRAX, oberoende av självrapporterad tidigare fraktur och andra kliniska riskfaktorer och bentäthet.

Slutsatser: Kotkompressioner diagnostiserade med VFA var associerade med lägre bentäthet i totalhöft, sämre fysisk hälsa och fysisk funktion hos äldre kvinnor. Milda kotkompressioner var oberoende associerat med incidenta MOF. Kotkompressioner diagnostiserade med VFA ökade 10-års sannolikheten för MOF väsentligt. VFA är en kliniskt värdefull metod för att diagnostisera relevanta kotkompressioner och förbättrar frakturrisk-bedömningen hos äldre kvinnor.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. **Johansson L**, Sundh D, Zoulakis M, Rudäng R, Darelid A, Brisby H, Nilsson AG, Mellström D, and Lorentzon M.

The Prevalence of Vertebral Fractures Is Associated With Reduced Hip Bone Density and Inferior Peripheral Appendicular Volumetric Bone Density and Structure in Older Women

Journal of Bone and Mineral Research. 2018 Feb; 33 (2): 250-260.

II. **Johansson L**, Sundh D, Nilsson M, Mellström D, and Lorentzon M.

Vertebral fractures and their association with health-related quality of life, back pain and physical function in older women

Osteoporosis International 2018 Jan; 29 (1): 89-99

III. **Johansson L**, Sundh D, Magnusson P, Rukmangatharajan K, Mellström D, Nilsson AG, and Lorentzon M.

Grade 1 Vertebral Fractures Identified by Densitometric Lateral Spine Imaging Predict Incident Major Osteoporotic Fracture Independently of Clinical Risk Factors and Bone Mineral Density in Older Women

Journal of Bone and Mineral Research. 2020 Oct; 35 (10): 1942-1951

IV. **Johansson L**, Johansson H, Axelsson KF, Litsne H, Harvey N C, Liu E, Leslie W D, Vandenput L, McCloskey E, Kanis J A, Lorentzon M.

Improved fracture risk prediction by adding VFA-identified vertebral fracture data to BMD by DXA and clinical risk factors used in FRAX

Osteoporosis International 2022 Published online 22 April

DOI: 10.1007/s00198-022-06387-x

Contents

Abbreviations

ABQ	Algorithm-based qualitative approach
ADL	Activities of daily living
ANOVA	One-way analysis of variance
AP	Antero-posterior
BMC	Bone mineral content
BMD	Bone mineral density (g/cm²), equal to aBMD
BMI	Body mass index (kg/m²)
BMSi	Bone material strength index
BMT	Bone microindentation testing
BMU	Basic multicellular unit of bone remodelling
BP	Bisphosphonates
BV/TV	Trabecular bone volume fraction (%)
CI	Confidence interval
CRF	Clinical risk factor
CV	Coefficient of variation (%)
DDD	Degenerative disc disease
DPA	Dual photon absorptiometry
DXA	Dual-energy X-ray absorptiometry
ECM	Extra cellular matrix
ESCEO	The European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis
ER	Oestrogen receptor
FLS	Fracture liaison service
FN	Femoral neck
FRAX	Fracture risk assessment tool
GC	Glucocorticosteroids
GH	Growth hormone
GSQ	Genant semi-quantitative method
HK	Hyperkyphosis
HR	Hazard ratio
HR-pQCT	High-resolution peripheral quantitative computed tomography
HRQL	Health-related quality of life
ICD 10	International Classification of Diseases, tenth revision
IDI	Indentation distance increase
IGF-1	Insulin-like growth factor-1
IOF	International Osteoporosis Foundation
ISCD	International Society for Clinical Densitometry

LS	Lumbar spine
µSV	Microsievert
MCID	Minimal clinically important difference
MCS	Mental Component Summary
MOF	Major osteoporotic fracture, i.e. fracture of spine, hip, upper arm, forearm, and sometimes pelvic fractures
NPR	National Patient Register
OPG	Osteoprotegerin
OC	Osteocalcin
OR	Odds ratio
PASE	Physical Activity Scale for the Elderly
PBM	Peak bone mass
PCS	Physical Component Summary
PTH	Parathyroid hormone
RANKL	Receptor activator of nuclear factor-κβ ligand
ROI	Region of interest
RPI	Reference point indentation
RR	Relative risk
SD	Standard deviation
SF-12	12-item short form health survey
SPA	Single photon absorptiometry
SUPERB	Sahlgrenska University Hospital Prospective Evaluation of Risk of Bone Fractures
SVH	Short vertebral height
SXA	Single X-ray absorptiometry
TBS	Trabecular bone score
TH	Total hip
T-score	Bone mineral density values in individuals expressed in relation to the young healthy population in standard deviation units.
vBMD	Volumetric bone mineral density (g/cm^3)
VF	Vertebral fracture
VFA	Vertebral fracture assessment
WHO	World Health Organization
z-score	BMD values in SD units that refers to age-related reference values
25-OH-D	25-hydroxyvitamin D

1. Introduction

Osteoporosis is a bone disorder, characterized by low bone mass and microarchitectural deterioration of bone tissue, resulting in increased bone fragility and consequent increase in fracture risk. The burden of osteoporosis-related fractures is growing globally, resulting in increased societal costs and suffering for the individuals affected.[1] Data on prevalence and incidence of osteoporotic fractures depends on which fracture definition is used. Recently published studies on osteoporotic fractures in Europe included fractures of the spine, hip, forearm and humerus (also called major osteoporotic fractures (MOF)), which increase progressively after the age of 50 and increase with decreasing BMD. In these studies, fractures of the pelvis, tibia, ribs, and other femoral fractures were also included in the analyses, due to the fact that these fractures are associated with low BMD, and both low-energy (fall from standing height or less) and high-energy trauma fractures were included (**Figure 1**).[1-5] In Sweden, just over 20% of women and 6% of men between 50 to 80 years of age are believed to have osteoporosis, in women this proportion rises from 6% in 50 year olds to 47% in 80 year olds.[6] 50-year-old Swedish women have the highest remaining lifetime risk of a hip fracture (25.1%) in the EU, a proportion that corresponds to a higher lifetime risk than that of stroke (20%).[1] Sweden was ranked third in 2019 for highest cost for osteoporotic fractures per capita compared with other EU countries (plus Switzerland and the UK).[3] In 2019, there were 124,000 new osteoporotic fractures in Sweden, generating a cost of about 1.4 billion euros. Fracture figures are expected rise to 161,000 in 2034. Every second woman and every fourth man in Sweden over the age of 50 will suffer an osteoporotic fracture during their remaining lifetime.[7] There is convincing evidence that osteoporosis and osteoporotic fractures are associated with increased mortality,[8-12] and in Sweden the number of deaths related to osteoporotic fracture exceeds the number of deaths related to lung cancer, diabetes or chronic lower respiratory diseases.[2] Older Japanese women with low FN BMD had more than twice the risk of mortality than women with normal BMD, independently of confounders, during a 12-year follow-up period.[8] Compared with other common health conditions such as septicaemia, cardiac dysrhythmias,

congestive heart failure, pneumonia and urinary tract infections and after adjustment for confounders, osteoporotic fractures, have the second longest length of stay (after septicaemia) and the highest average total hospital charges. [13]

The most common sites of fracture are hip, spine and wrist, of which vertebral fracture (VF) of the spine is the most common osteoporotic fracture, although only one third come to clinical attention.[14] The prevalence of VF in women over the age of 50 ranges between 20% to 26% in different studies [15-19], and prevalence may differ between countries with the highest prevalence in Scandinavia.[17] VF is one of the strongest predictors for new fracture.[20] There is evidence that long-term mortality risk following VF is increased by 82% [21], and that mortality increases due to numbers and severity of VFs.[12] Not only symptomatic but also asymptomatic VFs imply increased risk for subsequent fractures and mortality.[22] Apart from the individual suffering from VFs with pain, disability, impaired physical function, social isolation and depression,[23,24] the economic burden on the health care system is also significant.[13] Even though there are effective and cost-effective treatments for fracture prevention, the treatment gap is increasing.[3,25] Identifying VFs is one of many important measures which should be utilized to reduce the treatment gap. A method by which VFs can be identified is vertebral fracture assessment (VFA), and to explore this method's clinical usefulness is the main aim of this thesis.

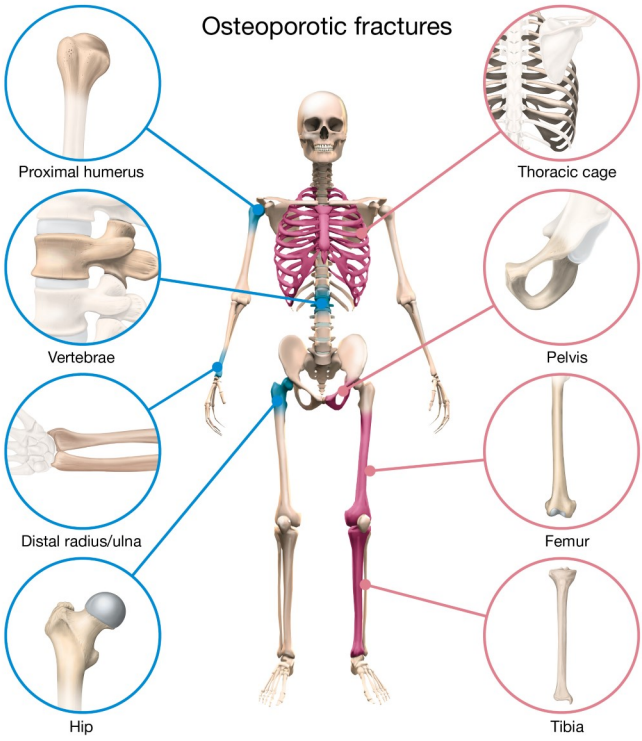


Figure 1. *Localisation of osteoporotic fractures. Blue circles denote major osteoporotic fractures (MOF) and pink circles denote other osteoporotic fractures.*

1.1 Bone

Bone tissue is composed of bone cells and extra-cellular matrix (ECM) (10 and 90% of total bone volume, respectively).[26] The three types of bone cells are the bone-resorbing osteoclasts (1-2% of the total bone cells), the bone-forming osteoblasts (4-6%) and the mechanosensory osteocytes (90-95%).[27] The matrix is formed by the osteoblasts and consists of 20% organic (type 1 collagen (90%), noncollagen proteins and proteoglykan) and 65% inorganic material (hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$), and water and lipids <15%. This mixture of organic and inorganic materials contributes to

the unique properties of bone, the combination of hardness and elasticity.[26] The dense and compact bone tissue forming the outer layer is called cortical bone and constitutes 80% of the total skeletal mass. Cortical bone is organized in so called osteons (Havarsian system), i.e. lamellae that are concentrically arranged around a central canal with a blood vessel. On the contrary, the inner bone tissue is organized in a rigid network of trabeculae, whose size and number and how they are distributed influence bone strength. This trabecular (or cancellous) bone constitutes 20% of the total skeletal mass but has a larger surface area (65-70%) compared with cortical bone, and is therefore more vulnerable to metabolic changes. The proportion of cortical and trabecular bone vary at different locations.[28] Locations with predominantly trabecular bone such as the vertebrae and metaphyses of the long bones are common sites for osteoporotic fractures.[2]

1.1.2 Bone modelling and remodelling

Bone modelling occurs mainly during skeletal development but also to a low extent during the remaining lifetime, and the process of bone formation and bone resorption may occur coupled or uncoupled.[29] Remodelling is the process within each basic multicellular unit (BMU) in which a balanced and coupled bone resorption and formation ensures maintained bone mass in the adult.[30] These BMUs are located along the bone surfaces, and the three different kinds of bone cells initiate activity on different signals. When remodelling is stimulated and the number of BMUs per bone surface area increases, bone turnover also increases. The rate of turnover in the adult skeleton is around 10% per year.[31] Where bone matrix has to be replaced (e.g. inferior quality, microfracture), preosteoclasts activate and fuse to mature osteoclasts (multinucleated). After 1-2 weeks of this resorption phase, osteoclasts are replaced by osteoblasts. During 2-3 months osteoblasts build bone, first unmineralized bone matrix (osteoid), which then becomes mineralized. Thereafter, the osteoblasts either transform into quiescent bone-lining cells on the newly formed bone, or undergo apoptosis, or become embedded within the matrix as osteocytes. The osteocytes have dendritic processes (canaliculi), with a "spider-shaped" appearance, with which they can reach the bone surface, communicate

with other cells and detect shifts in pressure and load. The shear stress in the fluid-flow in the canaliculi promotes e.g. the expression of osteoprotegerin (OPG, a glycoprotein), through the Wnt/β-catenin pathway.[32] OPG inhibits osteoclastogenesis. Osteocytes also secrete sclerostin, a protein that inhibits bone formation.[30] Recently it was found that receptor activator of nuclear factor-kB ligand (RANKL) is expressed by osteocytes.[33] When RANKL binds to the RANK receptor on osteoclasts and initiates osteoclastogenesis, bone resorption is stimulated. Thus, osteocytes regulate bone remodelling by acting on both formation and resorption.

With increasing age, an imbalance in bone remodelling develops, with bone resorption exceeding bone formation, which results in a gradual loss of bone mass and weakening of the bone. The remodelling process is influenced by a number of factors, including sex hormones, growth hormones, calcium-regulating hormones and several diseases.

Oestrogen binds to oestrogen receptors (ERs) to promote the expression of OPG that inhibits RANKL from inducing osteoclastogenesis.[34] In postmenopausal women, oestrogen levels decrease, resulting in downregulation of OPG expression and reduced inhibition of RANKL.[34] More RANKL can bind to RANK and increase osteoclastogenesis and bone resorption. Oestrogen also has an effect on mesenchymal stem cells to promote the differentiation from pre-osteoblasts to osteoblasts. If oestrogen levels are reduced, the impaired osteoblastogenesis can not compensate for the increased resorption, leading to increased bone loss with oestrogen deficiency, an important reason for the increased prevalence of osteoporosis in postmenopausal women (**Figure 2**).

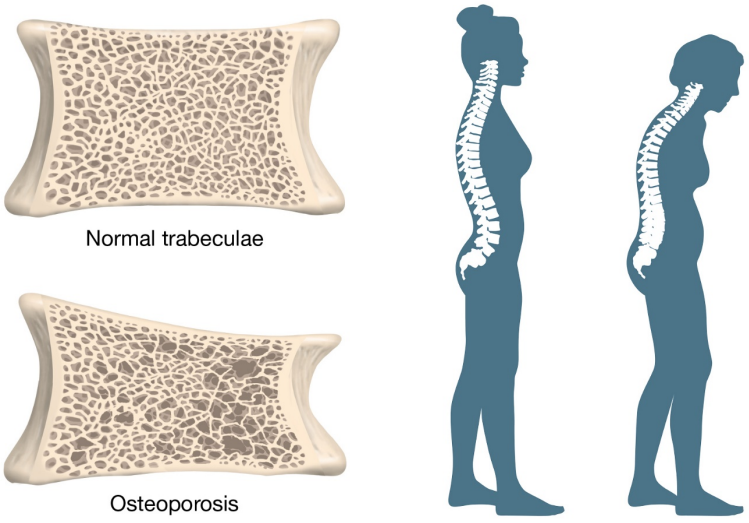


Figure 2. *Osteoporotic bone, resulting in vertebral fractures and change in overall body posture.*

Growth hormone (GH) from the pituitary gland stimulates the production of insulin-like growth factor I (IGF-I) in the liver and they are both important regulators of bone remodelling.[35] GH and IGF-I decline with age which may lead to decreased osteoblastic synthesis and impaired bone formation, contributing to the risk of osteoporosis in the elderly.

Also, calcium-regulating hormones are important regulators of bone remodelling. Most of the body's calcium (99%) and phosphorus (85%) are stored in the skeleton.[26]

Parathyroid hormone (PTH) is produced in the parathyroid glands and regulates the serum calcium concentration via effects on bone (calcium release by osteoblasts and osteoclasts), kidneys (re-absorption) and intestines (enhanced uptake).[30] PTH can stimulate both osteoblast maturation and osteoclastogenesis.

Calcitonin is produced by the parafollicular cells of the thyroid gland and has the opposite effect on serum calcium concentration from PTH. Secretion of calcitonin is stimulated by an increase in serum calcium level. To increase calcium deposition in bone, calcitonin inhibits osteoclast activity.[36]

Calcitriol (1.25 dihydroxycholecalciferol or vitamin D) is produced in the kidneys and is important for calcium homeostasis. In cases of low levels of serum calcium concentration, vitamin D increases calcium by increased uptake or re-absorption of calcium from the intestines and kidneys, or by stimulating the release of calcium from the bone. Vitamin D stimulates osteoblasts to release RANKL, which in turn stimulates osteoclasts, resulting in a secured serum calcium level at the expense of bone mass.[37,38] If the serum calcium level is adequate, mineral deposition in the bone is facilitated by the effect of vitamin D on osteoblasts. Thus vitamin D has a dual role in bone metabolism. Vitamin D deficiency and subsequent low serum calcium concentration result in elevated PTH. This state of secondary hyperparathyroidism leads to increased bone turnover and bone loss.[39]

1.3 Osteoporosis

1.3.1 Definition

The word "osteoporosis" was coined by the French pathologist Jean Lobstein (1777-1835) in 1820. He observed in autopsies an abundance of cavities in deteriorated bone and named this phenomenon osteoporosis from the Greek words *osteon* (bone) and *poros* (little hole).[40] During the last 200 years, the definition of osteoporosis has varied as research has progressed. The criterium "porous bone" has been followed by "loss of trabeculae" and "loss of calcium salts". In 1885, Gustav Pommer, a German pathologist, explained the difference between osteomalacia and osteoporosis. Osteomalacia is a disease with inadequate bone mineralization that leads to softening of the bones, despite a normal amount of bone. In osteoporosis, the bone is normally mineralized, but the overall amount of bone tissue is reduced.[41] During the twentieth century, when osteoporotic patients began to be offered treatment, the term "disease" was included in the definition. The modern definition of osteoporosis was introduced by the endocrinologist Fuller Albright in 1940.[42] He found a relationship between absent ovarian function and risk for fracture. When he administered oestrogen to postmenopausal women, it had positive effects on phosphorous

and calcium balance.[43] At that time it was known that atrophy of bone could be a result of either lack of stress and strain on bone, or ageing (senile osteoporosis). A third category was called "idiopathic osteoporosis". Albright found that in this group (< 65 years), the majority were women, they were postmenopausal or had undergone surgical menopause. Hence he defined the condition as *postmenopausal osteoporosis*.[44] In the 1980s, different techniques were used to measure bone mass or density,[45,46] and the role of trabecular microstructure in the pathogenesis of osteoporosis was clarified.[47] These discoveries were the basis for a Consensus Development Conference to defining osteoporosis as a "disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk".[48] The WHO accepted this definition in 1994.[49] In 2000, the NIH Consensus Development revised the definition and defined osteoporosis as:

"a *skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture."* [50]

1.3.2 Bone mass measurements

1.3.2.1 Dual-energy X-ray absorptiometry

Bone strength depends on bone mass and bone architecture, parameters not easy to assess in vivo, but correlated with bone mineral density (BMD).[51] Dual-energy X-ray absorptiometry (DXA) is the successor of single photon (and x-ray) absorptiometry (SPA,SXA) and dual photon absorptiometry (DPA) and was first introduced in 1987. It provides a two-dimensional image of the lumbar spine (LS), hip, forearm and total body (**Figure 3**).[52] At the hip, the most common regions of interest (ROIs) are the femoral neck (FN) and total hip (TH). DXA measures bone mineral (calcium hydroxyapatite) density (BMD) defined as the mass of the bone mineral content (BMC) (g) in the ROI divided by the area (cm^2) of the same ROI, resulting in the areal BMD with the unit g/cm^2. To interpret the results

from a DXA exam, the results are compared with a normal reference population matched for age, sex, and ethnic origin. BMD results are expressed as the difference from the mean BMD for young adult or age-matched normal populations, and this difference is expressed as numbers of standard deviations (SDs) from the mean, also expressed as T-score when compared with young adults and Z-score when compared with age-matched normal populations.

X-rays are beams of photons that transmission through the body and attenuate when passing through different tissues. The amount of attenuated radiation depends on: 1. the energy of the photon, 2. the composition and density of the material that the beam passes through, 3. the thickness of the material. The denser the tissue, the more electrons it contains, and the more photons are attenuated. The density of the tissue can be measured by knowing the degree of attenuation of the photons in the x-ray beam. By using two different photon energies, where the low-energy (30-50 keV) has higher attenuation for bone tissue than for soft tissue, and the high energy (>70 keV) has similar attenuation for bone and soft tissue, the density of bone can be determined. The radiation dose for a spine and hip image is low, around 1-10 μSv (about the same as one day of natural background radiation), and the scan time is less than a minute. Even though DXA is the gold standard for determining BMD in clinical practice, there are some limitations with the technique. DXA results may be confounded by a number of factors, including bone size (falsely high in larger bones due to the two-dimensional imaging), aortic calcification and degenerative remodelling.[53]

Figure 3. *DXA device Discovery A S/N 86491; Hologic, Waltham, MA, USA.*

1.3.2.2 Trabecular bone score

DXA does not measure microarchitecture, and to overcome this limitation, trabecular bone score (TBS) was developed and presented in 2008 as a complement to BMD measurements.[54] TBS is a parameter reflecting the trabecular bone microstructure in the LS assessed in conjunction with DXA. TBS is obtained by generated variograms from grey-level variations of the two-dimensional image by DXA, and reflects the heterogeneity of the bone.[54] A high TBS value means that the bone microarchitecture is dense and well-connected, with little space between the trabeculae, while a low TBS value means that the bone microarchitecture is incomplete, with large spaces between trabeculae (**Figure 4**).[55] TBS is a predictor of fracture risk independently of BMD [56] and also independently of clinical risk factors (CRFs) used in the Fracture Risk Assessment Tool (FRAX).[57] FRAX is further described in chapter 1.5.2. TBS has been used in FRAX since 2016 to adjust the probability of fracture, and according to the 2019 International Society for Clinical Densitometry (ISCD) Official Position, TBS may also be used in monitoring anabolic treatment.[58]

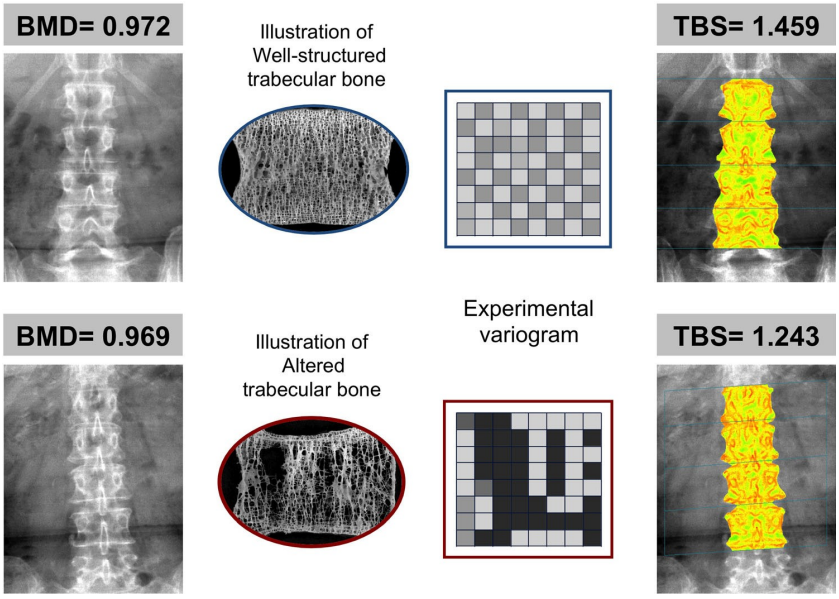


Figure 4. *Representation of the TBS principles and an example in which the TBS appears to be independent from BMD. Upper panel shows BMD and TBS images of a 73-year-old woman, with a BMI of 24.2 kg/m2, lumbar spine BMD of 0.972 g/cm2, and TBS of 1.459. Lower panel shows BMD and TBS images of a 74-year-old woman, with a BMI of 24.3 kg/m2, lumbar spine BMD of 0.969 g/cm2, and TBS of 1.243. Although the images of the bone architecture and the experimental variogram are illustrations and do not represent actual images from these patients' skeleton, they were placed here to demonstrate the TBS principles: more numerous and connected and less sparse trabeculae translate into a high TBS value, whereas a low trabecular number and connectivity and high trabecular separation translate into a low TBS.* ***With kind permission of John Wiley and Sons.***[55]

Compared with DXA, conventional x-ray is inferior in detecting osteoporosis. It is estimated that BMD has to decrease approximately 30% before the bone loss is recognised in conventional radiographs.[59] In the 1990s, there were some important developments of the DXA methodology: fan beam instead of pencil beam enabling decreased scanning times; implementation of a rotating C-arm making it possible for the patient stay in supine position; and improvements in image resolution. These advances contributed to the development of vertebral fracture assessment (VFA), a method by which VFs are identified from the lateral spine image.[60] VFA is described further in chapter 1.5.3.

1.3.2.3 QCT and pQCT

Although DXA is the "gold standard" for diagnosing osteoporosis, it has some limitations. DXA provides a two-dimensional analysis and measures the bone mineral content (BMC) in a specific area. BMD (aBMD) is calculated by dividing BMC by the area (g/cm^2). DXA does not measure volume or depth of the bone resulting in a falsely high BMD for larger bones. DXA does not provide measurements of bone geometry and can not distinguish trabecular bone from cortical bone. During the 1980s, several studies examining trabecular bone microstructure, mainly based on histomorphometry, showed how the trabecular bone microstructure deteriorates in ageing and in osteoporosis, and the importance that bone microstructure has on bone strength and future fractures.[47,61-64] Bone strength is dependent on bone density, bone geometry and bone quality (microstructure), and this knowledge led to the introduction of the concept of bone quality in the definition of osteoporosis.[48,65]

Quantitative computed tomography (QCT), an x-ray-based technique providing cross-sectional images, was originally developed in the 1970s. At the beginning, the trabecular bone density was measured two-dimensionally and the method was applied to the lumbar spine.[66] Technical improvements over the last decades have made it possible to acquire three-dimensional images not only at the LS but also at the hip, and the acquisition time for this central QCT has become shorter.[67,68] In contrast to DXA, QCT measures true volumetric BMD (mg/cm^3), has the ability to analyse the trabecular and cortical bone separately, and is not confounded by degenerative changes in the spine or bone size. The radiation dose for spine and hip is around 500-800 µSv, a rather high dose compared with central DXA yielding around 1-10 µSv. Whole-body CT scanners are large and expensive, and osseous fat is potentially a source of error when using central QCT. To overcome the disadvantages of central QCT, peripheral quantitative computed tomography (pQCT) was introduced in the late 1980s, designed to measure peripheral bones, e.g. the distal forearm (radius) and the distal leg (tibia), with a lower radiation dose, < 3 µSv in a single-slice protocol, which increases in multiple-slice protocols.[68]

1.3.2.4 High-resolution peripheral quantitative computed tomography

When pQCT first was introduced, trabecular and cortical density could be assessed but not the three-dimensional microstructure.[69] A new method to analyze the three-dimensional structure of trabecular bone, using a non-invasive bone biopsy, was introduced in 1994.[70] The nominal isotropic resolution was 170 µm in these initial imaging systems. With additional advances, a new non-invasive high-resolution peripheral quantitative computed tomography (HR-pQCT) system made it possible to assess volumetric BMD and the microstructure of trabecular and cortical bone at the distal radius and tibia with a nominal isotropic voxel size of 82 µm.[71,72] The radiation dose is almost equivalent to central DXA of around 5 µSv. The method has been validated against micro CT and DXA and has good reproducibility.[73]

1.3.3 Bone strength by bone microindentation

Indentation is a method whereby a hard tip is pressed into the bone tissue with a known force.[74,75] In 2010, a new technique for bone microindentation testing (BMT) made it possible to quantify the mechanical properties of bone at a tissue-level (*in vivo*).[76,77] The ability of bone to resist microfracture can be assessed by measuring the indentation distance performed by a reference point indentation (RPI) instrument, and the deeper the cavity the more susceptible the bone is to fracture. Bone material strength index (BMSi) is a parameter related to this resistance to indentation in bone tissue. However, studies investigating the relationship between resistance to indentation and the occurrence of fracture have found differing results, with one showing no relationship [78], while another showed that patients with an osteoporotic fracture, compared with women without, had significantly lower BMSi.[79] The clinical utility of bone microindentation is still controversial [80] and whether or not it can accurately measure cortical stiffness and predict fracture is unclear. [81]

1.3.4 Quantitative ultrasound

Quantitative ultrasound (QUS) is a non-radiation technique that measures: 1. the attenuation of ultrasonic waves passing through the tissue, Broadband Ultrasound Attenuation (BUA, dB/Mhz), reflecting the bone density and architecture, and 2. the velocity of the ultrasonic waves through the tissue, the Speed of Sound (SOS, m/s), reflecting the bone density and elasticity.[82] These parameters do not measure BMD. QUS is used at peripheral sites (heel, finger, tibia). The advantages of QUS are that the devices are portable and non-ionizing. However, disadvantages including lack of reference databases, differences in precision between devices, and difficulties in comparing devices have limited the clinical utility of QUS.[83] Even though heel QUS may predict osteoporotic fractures in postmenopausal women [84] others have shown modest correlation of QUS at peripheral sites and BMD at central sites ($r = 0.3$; $P < 0.0001$).[85]

1.3.5 Diagnosis

The WHO-Classification from 1994 is still the "gold standard" for diagnosing osteoporosis, and a DXA of the spine, hip or mid-radius is required.[49] Osteoporosis is present when T-score $\leq$ 2.5 SD, that means when the BMD is equal to or less than 2.5 SD from the mean in a population of young white adult women. The cutoff value of -2.5 SD was arbitrarily set because at that level, 30% of postmenopausal women would be diagnosed with osteoporosis, which coincides with the lifetime risk of fracture at the spine, hip or forearm.[86] The WHO Classification is presented in **Figure 5**.

	T-score (SD)
Normal	-1.0 or higher
Osteopenia	Between -1.0 and -2.5
Osteoporosis	-2.5 or lower
Severe osteoporosis	-2.5 or lower with fracture

Figure 5. *WHO Classification of Postmenopausal Osteoporosis.*[49]

1.3.6 Determinants of bone loss

The amount of bone mass at any time during adult life depends on both the rate of bone loss and the peak bone mass (PBM). PBM is the maximum bone mass acquired during lifetime and this occurs at different times depending on gender and skeletal site.[87,88] At birth there is no difference in bone mass between boys and girls, but during puberty males gain more bone mass, and the bone size and cortical thickness become greater than in females, to some extent due to the more prolonged period of pubertal maturation. However, although the areal BMD is greater among males, there is no significant difference between males and females in the volumetric trabecular density at the end of skeletal maturation.[87] Hip BMD peaks before spine BMD[89] and longitudinal data shows that PBM is achieved between 20-25 years of age [90], occurring earlier in females than in males.[91] The most important factor to influence PBM is heredity. 60-80% of variance in PBM can be explained by genetic factors. Other factors affecting PBM are hormones, nutrition and physical activity.[92,93] The risk of osteoporotic fracture is related to the maximum bone acquired minus the bone loss due to ageing.

Bone loss accelerates around the menopause and averages 2% per year over the next 5-10 years. During this period, bone loss follows an exponential decline. Loss is greatest in the early postmenopausal years, levels off thereafter, and finally returns to the premenopausal level.[94] The rate of bone loss in men is low, probably 3-5% per decade. The rate of bone loss is more rapid in the spine (cortical and cancellous bone) than in the forearm (largely cortical). By the age of 75, women have lost about the same amount of bone in the peripheral and the axial skeleton. The more rapid losses from the axial skeleton may account in part for the earlier presentation of VFs compared with hip fracture, which characteristically occurs later in life. The rate of postmenopausal bone loss varies widely and ranges from less than 1% to more than 5 % per year (from site to site and from woman to woman). Little or no relationship has been found between bone mass at maturity and the rate of bone loss. In an osteoporotic patient about 10% of the skeletal mass consists of cancellous bone. However, the surface area of cancellous bone is greater than that of cortical bone [95], and because of the high surface-to-volume ratio of cancellous bone tissue, disorders

such as osteoporosis more commonly affect trabecular sites earlier in the disease process.[95]

1.4 Vertebral compression fracture

1.4.1 Epidemiology

The epidemiology of VF is well studied even though it is challenging due to the different definitions of VFs and that a majority of individuals with VF, two-thirds, are asymptomatic. About 25% of women over 50 years of age will sustain a VF and the prevalence increases with age from 6% at 50-54 years of age to about 40% at 85-89 years of age, although prevalence is countryspecific.[15] VFs result from minor trauma during day-to-day activities such as lifting, bending forwards, and climbing stairs, and only about 30% are related to falls.[96] VFs are related to increased mortality [97], impaired health-related quality of life (HRQL)[24], and increased risk of subsequent fractures.[20] In a large study of postmenopausal women, the risk of death was increased 8 times among women with VF compared with women without, also after adjustment with factors known to influence mortality.[98] In a population-based cross-sectional study from Tromsø, women with prevalent VFs had increased risk of back pain and lower HRQL compared with women without fracture, also after adjustment, [99] and lower physical HRQL in women with clinical VF may persist for as long as 18.9 years after time of fracture.[100]

1.4.2 Classification

There are different methods in classifying VFs.[101] Hurxthal was the first to describe how to measure vertebral heights in wedge fractures, in 1968. Since then, different methods of quantitative morphometry (QM) have been described for identifying VFs. With QM [15,102-104], the vertebrae dimensions are measured by 6-point morphometry, and QM has been utilized in many epidemiological and interventional trials, even though the disadvantage of QM is its inability to discriminate between fractures and other

causes of vertebral deformities.[105] To avoid misclassification, Genant *et al*.[106] introduced the Genant semi-quantitative method (GSQ), in which the vertebrae T_4 to L_4 are first assessed visually for height loss and then evaluated for fracture status, defined by signs of end plate depression, buckling of cortical margin and lack of end plate parallelism. Once classified as fractured, the fracture is graded and divided into wedge, biconcave or crush by visually comparing it to a template chart (**Figure 6**). Height loss is compared with other heights of the same and/or adjacent vertebrae and divided into grade 1 (mild), grade 2 (moderate) or grade 3 (severe) (20-25%, 25-40%, and >40%, respectively).[106] In 2004, Jiang et al. introduced the algorithm-based qualitative approach (ABQ) in which VFs are identified when the vertebral endplates are fractured, regardless of whether there is height reduction or not (**Figure 7**).[107] To examine whether different methods for identifying VF at baseline have an impact on subsequent VF risk in postmenopausal women, Melton et al.[108] evaluated baseline deformities by several different methods in 512 women, using conventional radiographs. In that study, incident VFs were defined as height reduction of 20%. Mild fractures identified at baseline, using two different QM methods (15-20% height loss (Melton[15]) or reduction of 3 SD from the expected mean from normal women (Eastell[102])), did not predict subsequent VFs, whilst the "prevalence" QM method (reduction of 3 SD not only compared with each vertebra but also compared with predicted values from four adjacent vertebrae (McCloskey[103] and Black[109])) and ABQ predicted subsequent fractures, possible due to less false positives. GSQ was not included in this study. Depending on which method was used the prevalence of VFs ranged from 3 to 90%.[108]

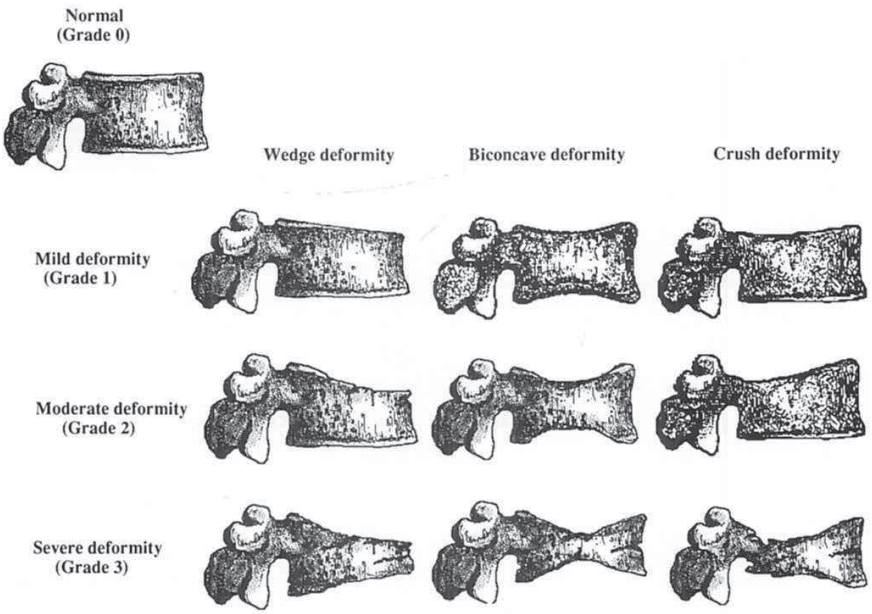


***Figure 6**. Genants semiquantitative classification **with kind permission of John Wiley and Sons**.*[106]

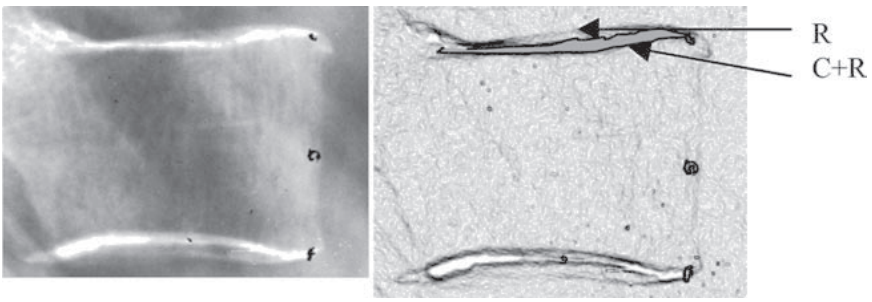


***Figure 7.** Appearance of vertebral endplates in a normal vertebra. R represents the vertebral ring line, C+R represent the central endplate within the vertebral ring overlapping the vertebral ring line. **With kind permission of Springer Nature.** [107]*

1.4.3 Vertebral fracture cascade

Most individuals who fracture do not have osteoporosis defined by DXA. Only 39% of the individuals with VF had osteoporosis by DXA at the lumbar spine, and only 25% by DXA of the total hip.[110] However, individuals

with VF are mostly older women who to a larger extent have spinal degenerative remodelling, resulting in unreliable LS BMD measurements. Therefore, TBS by DXA is most likely a more reliable parameter assessing bone strength in the LS in older women.[111] TBS is further explained in chapter 3.4.1.1. Among the women with an incident VF, 19% sustained a new incident VF in the following year [112], and considering that 60-80% of the vertebral bone strength can be explained by BMD there must be other factors contributing to bone fragility and fracture risk.[113] Beyond microarchitecture (e.g. the trabecular lattice) and macroarchitecture (the size of the vertebra), well-known factors affecting bone strength, there are other parameters contributing to the frailty of the spine, which all together can result in the vertebral fracture cascade (**Figure 8**).[114] For instance, an increased thoracic kyphosis (hyperkyphosis (HK)), due to anterior wedge VF, may increase the pressure on the vertebrae anteriorly, altering the biomechanics (smaller lever arm, i.e. distance between the erector spinae muscle and midmost of the vertebra), and increasing the probability for another fracture. The prevalence of HK in older women is around 40% but only one third of them have VF, and the most common reason for HK is degenerative disc disease (DDD). In a clinical trial in postmenopausal women with osteoporosis, the relative risk (RR) for subsequent VF was 1.70 (95% CI: 1.32-2.21) for those with high kyphosis compared with those with low kyphosis. This association remained after adjustment with prevalent VFs, age, BMI and spine BMD (RR 1.42 (1.08-1.86)), indicating that HK is an independent risk factor for future VF.[115] The consequences of HK that may contribute to the vertebral fracture cascade are increased spinal loads, decreased thoracic extensor muscle strength, unstable gait and decreased physical function.[116] Chronic pain may lead to decreased activity and immobility, resulting in bone and muscle loss. In a normal intervertebral disc, the load is evenly distributed over the end plate with only minor load on the posterior elements of the vertebra. In DDD, load-bearing is shifted more to the posterior elements in upright position, resulting in loss of bone anteriorly due to stress shielding, and making the vertebra vulnerable to fracture during forward bending.[117] VFs are independently associated with adjacent disc degeneration due to e.g. mechanical stress and reduced blood flow and nutrients from the collapsed vertebra.[118] Disc degeneration in

turn causes bone loss (due to stress shielding, see above) – predisposing VFs – and this cycle contributes to the vertebral cascade.

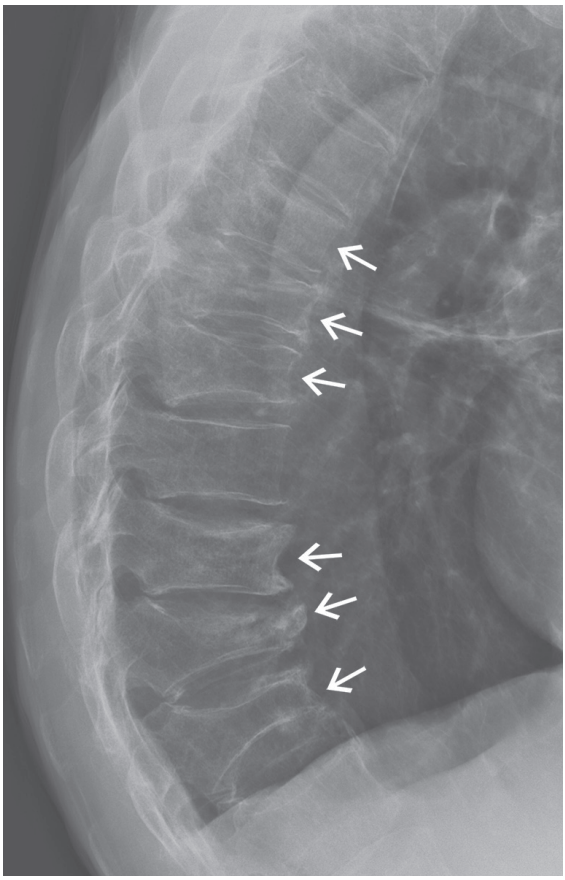


Figure 8. *Lateral radiograph showing vertebral fracture cascade with fractures of many contiguous or near-contiguous vertebrae.* ***With kind permission of Quantitative Imaging in Medicine and Surgery.***[119]

1.4.4 Differential diagnoses

A vertebral deformity is not always a VF. It is important to have knowledge about other possible causes behind a deformed vertebra.

Physiological wedging

Mild anterior wedging of thoracic and upper lumbar vertebrae and mild posterior wedging of lower lumbar vertebrae (L4-L5) are normal physiological features resulting in a spinal curvature with thoracic kyphosis and lumbar lordosis (**Figure 9**).

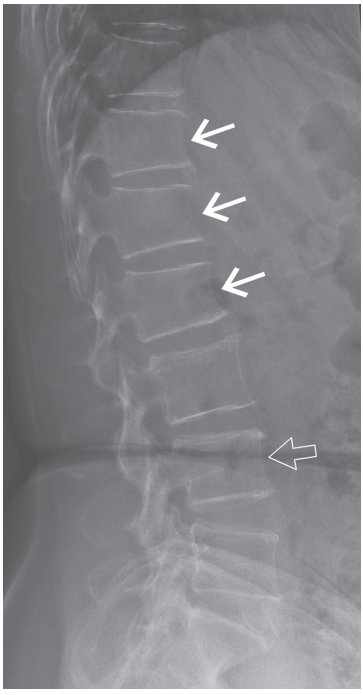


Figure 9. *Distinguishing between physiological wedging of the T12, L1 and L2 vertebral bodies (arrows) and a mild fracture is difficult in this case. Anterior vertebral body height is not quite reduced to >20% of what you would normally expect it to be (given expected physiological wedging at this level). There is also short vertebral height of the L4 vertebral body (open arrow)in that the height is not reduced to more than 20% of what you would normally expect it to be at this level.* ***With kind permission of Quantitative Imaging in Medicine and Surgery[119].***

Short vertebral height (SVH)

SVH is probably the most difficult differential diagnosis to distinguish from a mild VF. SVH is a reduction in expected height of up to 20% and

occurs with increasing age (**Figure 9**). In women between about 30 and 70 years of age, the combined anterior heights from T4-L5 decrease about 1.5 mm/year, while middle and posterior heights decrease about 1.2 mm/year.[120] However, SVH is not associated with low BMD.[121]

Scheuermann's disease

In Scheuermann's disease an uneven growth of the thoracic vertebrae, in which the posterior border grows more than the anterior border, results in wedged vertebrae and kyphosis. Most commonly, T7-T10 are affected and may be misinterpreted as multiple VFs. Other signs in Scheuermann's disease are elongated vertebrae, reduced disc height and endplate indentations (**Figure 10**).

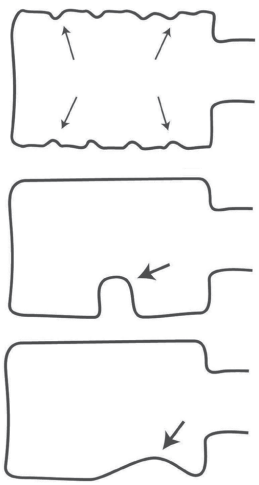


Figure 10. *Schematic diagram showing endplate impressions caused by (A) Scheuermann's disease; (B) Schmorl's node and (C) Cupid's bow deformity.* ***With kind permission of Quantitative Imaging in Medicine and Surgery.***[119]

Degenerative changes and scoliosis

With increasing age, the presence of osteophytes, narrow disc spaces and lower anterior height can complicate the assessment of vertebral deformities. A wedge VF can be distinguished from degenerative lower anterior height if not only the anterior/posterior height ratio is lower but also the mid/posterior height ratio.[122] Scoliosis is common in the elderly spine and on the lateral spine image the obliquity of the vertebrae, resulting in elliptical shapes of the endplates, may be misinterpreted as biconcave VFs (**Figure 11**). It is therefore often useful to perform an anteroposterior (AP) projection of the spine, to become aware of any scoliosis.

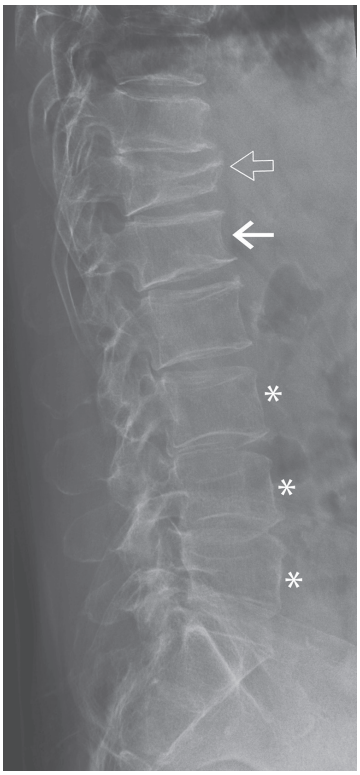


Figure 11*. There is a severe osteoporotic fracture of the T12 vertebral body (open arrow) with a mild osteoporotic fracture of the L1 vertebral body (arrow). There is a lumbar scoliosis with obliquity of the lower three lumbar vertebrae (*).****With kind permission of Quantitative Imaging in Medicine and Surgery.***[119]

Schmorl's nodes

Schmorl's nodes are indentations of the disc into the endplates, and are common in degenerative spines. A larger Schmorl's node may look like a VF, however, unlike VF, Schmorl's node has a well-defined sclerotic contour and does not involve the whole endplate (**Figure 10**).

Cupid's bow deformity

Cupid's bow deformity is a developmental variant of the inferior endplate (less frequently the superior endplate), most common in the lower lumbar spine and not related to osteoporosis.[123] The absence of cartilage focally on the 2/3 of the posterior inferior endplate impairs growth of the vertebra, resulting in a deformity that on the AP projection resembles the curve in the middle of the upper lip, the Cupid's bow. And there may also be developmental variant of the endplates anteriorly (**Figures 10 and 12**).

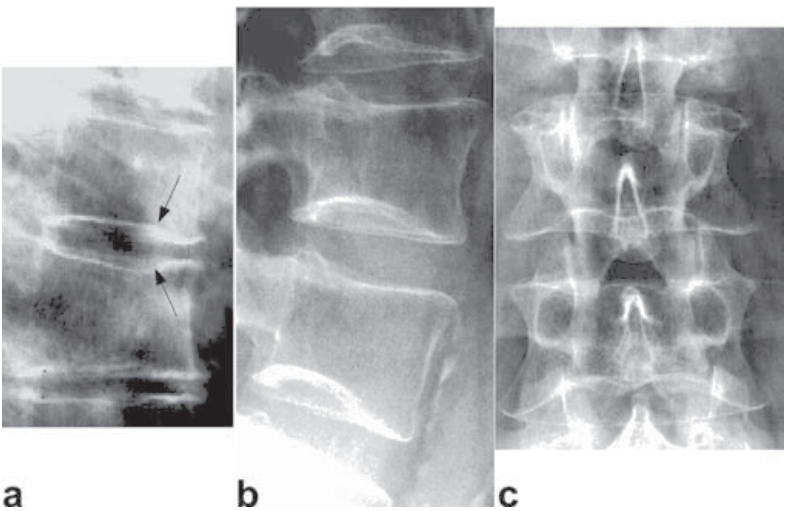


Figure 12. *Developmental deformity. a The inferior endplate of vertebra T7 and the superior endplate of T8 are deeper anteriorly (arrows). These endplates appear symmetrical about the intervertebral disk. b The endplate is much deeper at the posterior end of the inferior endplate of L3. c The AP view shows that the change is caused by a 'Cupid's bow' developmental deformity.* ***With kind permission of Springer Nature.***[107]

1.5 Assessment of fracture risk

BMD by DXA has been the gold standard historically for diagnosing osteoporosis and predicting fractures. However, studies have shown that fewer than half of all fractures occur in osteoporotic women.[110,124] Instead, the majority of fractures occur in osteopoenic individuals, and the primary cause for this may be the larger number of individuals at risk in the osteopoenic population.[125] Age and BMD are the strongest independent predictors of fracture.[126] A common way of computing relative risk is to compare the individuals with the risk factor with individuals without the risk factor. However, in the clinical setting it is more useful and appropriate to estimate the absolute risk of fracture for an individual.[126] The absolute risk of fracture is higher in the older woman than in the younger woman, at any given BMD, since age contributes independently of BMD and other risk factors to fracture risk. A challenge with DXA-derived BMD is that depending on which technique (fan or pencil beam) and manufacturer are used, as well as which site is measured, the resulting BMD will be differently associated with fracture risk.

In the early 2000s, it became more accepted to distinguish the diagnostic thresholds for osteoporosis (a T-score of -2.5 or less) from intervention thresholds, because the risk of fracture varies at any given BMD, according to presence of other risk factors for fracture.[127] To enhance the probability of finding individuals at high risk of fracture, the intervention thresholds should be based on fracture probabilities (the absolute risk) over a given period of time, instead of T-score alone. The rationale behind the development of the Fracture Risk Assessment Tool (FRAX) was to provide a tool for the calculation of 10-year probability of MOF and hip fracture, based on age, sex, BMI, and a number of clinical risk factors (CRFs).[128,129] FRAX is further described in chapter 1.5.2. The 10-year time horizon was considered appropriate because a normal treatment duration with osteoporosis medications usually lasts for 5 years with a remaining effect for another 5 years.[6,127,130] The 10-year fracture probability takes into account age, life expectancy and the presence of CRFs. One advantage of using fracture probability in risk assessment is that other risk factors, the ones that contribute beyond what is provided by BMD, can be incorporated

(with or without BMD) in the risk assessment. By combining risk factors and BMD, the prediction of osteoporotic fractures can be improved.[6,131,132]

1.5.1 Clinical risk factors

Age and BMD

Both advanced age and low BMD are well-known risk factors for fracture.[46,110] For each SD decrease in BMD, the risk for fracture increases by a factor of 1.4-2.6 and is comparable to the use of blood pressure to predict stroke.[133] However, this association is not independent of age. In a meta-analysis of 12 cohorts, the results showed that for 65-year-old-women, each SD decrease in BMD increases the risk of any osteoporotic fracture 1.38 fold and for 85 year-old-women 1.65 fold.[134] On the contrary, for hip fracture, the gradient of risk (relative risk (RR)/SD) decreased with age, and the reason for this is not known. However, the 10-year probability for hip fracture (the absolute risk) increased with age.

Body mass index (BMI)

In a meta-analysis on data from almost 60,000 men and women from 12 prospective population-based cohorts, BMI (weight/height^2) was associated with fracture risk, but not linearly, and partly dependent on BMD.[135] A BMI of 20 kg/m^2 compared with a BMI of 25 kg/m^2 was associated with almost double risk of hip fracture, without adjustment with BMD. When a BMI of 30 kg/m^2 was compared with a BMI of 25 kg/m^2 there was a reduction in hip fracture risk of 17%. The increased risk of hip fracture with a low BMI remained after adjustment with BMD.

Previous fracture

A previous fracture increases the risk of a new fracture almost twofold, independently of BMD.[136] The risk differs between different locations of prior fracture. A prior VF infers a specifically strong risk with a fourfold increased risk of a new VF.[20] The fracture risk is greatest within the first

two years after the first fracture and then wanes with time, but is still higher compared with those without prior fracture after more than ten years.[137]

Heredity, smoking, alcohol, glucocorticoids, secondary causes of osteoporosis

Several meta-analyses have investigated the risk of fracture for different CRFs. Parental history of any fracture increased the risk of hip fracture by around 50% and a parental hip fracture more than doubled the risk of hip fracture, independently of BMD.[138]

Compared with non-smokers, current smoking increased the risk of hip fracture by 60% after adjustment for BMD. Dose dependent associations with fracture risk could not be evaluated due to differences in how data on smoking habits were collected.[139]

If alcoholic beverages were consumed to a lesser extent than 2 standard units (1 unit=8 g alcohol) per day, fracture risk was not significantly increased. Intake of more than 3 standard units per day almost doubled the risk of hip fracture, independently of BMD.[140]

For previous oral glucocorticoid users, the relative risks at the age of 50, compared with non-users, were 1.98, 2.63 and 4.42 of any fracture, osteoporotic fracture and hip fracture respectively, independently of BMD and prior fracture, although the risk decreased with increasing age.[141] In another meta-analysis of 66 studies, there was a dose-dependent association between use of oral glucocorticoids and risk of fracture. Rapid loss of BMD and increased risk of fracture were observed within 3 to 6 months after start of treatment, and daily doses of ≥5 mg of prednisolone or equivalent was regarded as a risk factor for fracture during the treatment period.[142]

Rheumatoid arthritis is associated with increased fracture risk independently of BMD. Other secondary causes of osteoporosis with significant associations with fracture risk are inflammatory bowel disease, type 1 diabetes, thyroid diseases, prolonged immobilisation, and untreated hypogonadism, but the risk increase observed with these conditions was not independent of BMD.[128]

1.5.2 The Fracture Risk Assessment Tool (FRAX)

In 2008, the Fracture Risk Assessment Tool (FRAX) was introduced.[128,129] It is a web-based calculator, free of charge and easy to use (**Figure 13**).[143] Based on age, sex, body mass index (BMI), and CRFs such as parental hip fracture, prior fragility fracture, smoking, systemic glucocorticoid use, rheumatoid arthritis, excess alcohol intake, and other causes of secondary osteoporosis, the 10-year fracture probability of MOF (clinical spine, hip, proximal humerus or distal forearm) and hip fracture can be calculated with or without BMD. FRAX is currently available in 77 countries covering more than 80% of the world population, and has been validated in 11 independent cohorts.[144] FRAX does not take into account the glucocorticoid dose, type or recency of fracture, or spine BMD, but it is possible for the clinician to adjust the FRAX risk by using calculated ratios or percentage adjustments.[145-147] Adjustments for dosage of alcohol and smoking, multiple fractures or fall tendency are lacking, and therefore, beyond the FRAX guidance, the clinician's individual assessment is important.

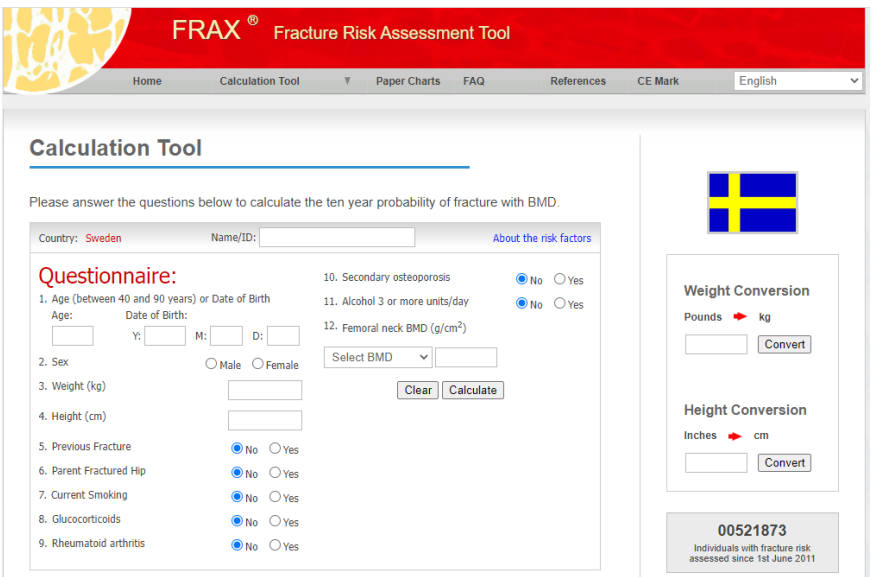


Figure 13. *Screen shot from* https://www.sheffield.ac.uk/FRAX

1.5.3 Vertebral fracture assessment

Spinal imaging is required to identify VFs and in the clinical setting conventional x-ray of the thoracic and/or lumbar spine is the most commonly used method to detect VFs in patients seeking medical attention.

VFA is however a suitable method to identify both symptomatic and asymptomatic VFs, and the benefits of VFA compared with conventional x-ray are several, including lower radiation exposure (about three µSv vs. about 600 µSv for a lateral lumbar spine x-ray), greater convenience for the patient as VFA is performed at the same time as DXA measurements [148-150] and lateral spine image is performed for both thoracic and lumbar spine. Using conventional x-ray for either the thoracic or lumbar spine may result in a neglected VF at the level not being examined. Several studies during the last 20 years have demonstrated the reliability of VFA to identify VFs, and VFA is now an established method with high accuracy, although inferior image resolution and poor visualization of thoracic spine levels above T7 are limitations of VFA compared with conventional x-ray. [60,151-153] In conjunction with the DXA exam, a lateral spine image is performed with the participant in either supine or decubitus position depending on which device is used. The fourth lumbar vertebra is usually marked by the DXA operator after looking at the AP image of the lumbar spine. By using the software programme Physician's viewer (Hologic), the grey scale, magnification, contrast and brightness can be adjusted, and the ability to assess each vertebra is improved. Six markers are placed on each vertebra T_4 to L_4 at the upper and inferior endplates at three places, anterior, middle and posterior.[154] To assess the possible presence of scoliosis, the lumbar AP spine image and whole-body image can be used. Scoliosis may cause rotated vertebrae, which may be misinterpreted as biconcave fractures. Differential diagnoses of other morphologic deformities are: short vertebral height, Scheuermann's disease, degenerative scoliosis, Schmorl's nodes, and Cupid's bow deformity, described in chapter 1.4.4.[119] The VFs can be classified according to the GSQ method [106], as mild, moderate or severe (height reduction 20–25%, > 25–40% and > 40%, respectively), and the type of fracture – wedge, biconcave, or crush – is recorded. **Figure 14** and **Figure 15 a-c** show a woman with a severe VF

but without scoliosis and a woman with scoliosis but without fractures, respectively.

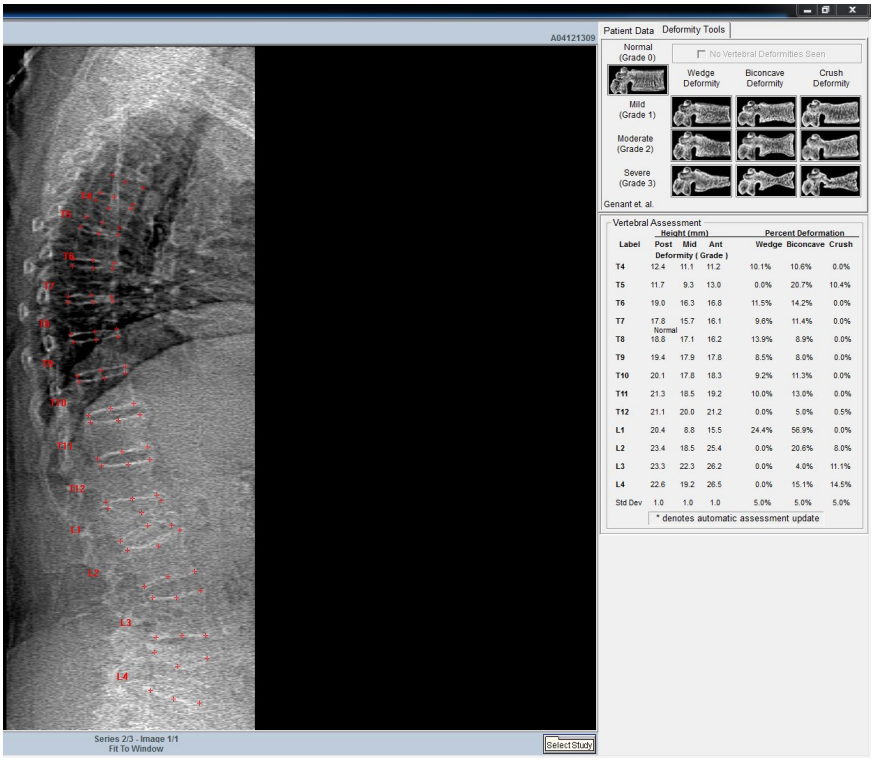


Figure 14. *Lateral spine image by DXA (Hologic) of a 75-80 year-old-woman without scoliosis but with a severe VF at L1 and degenerative changes at T10-T12. VFA was performed using the software programme Physician's Viewer (Hologic).*

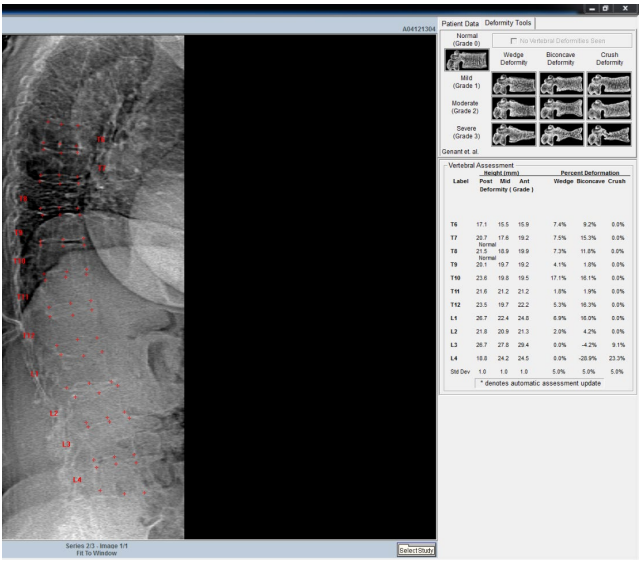
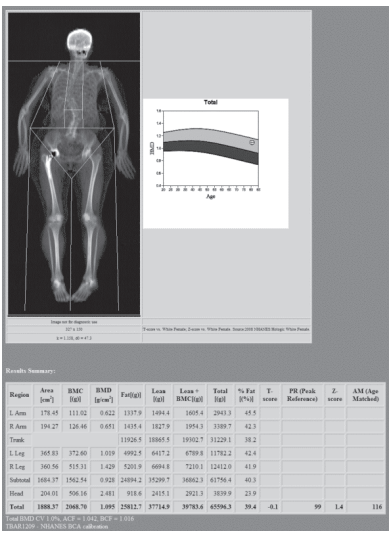


Figure 15 a. *Lateral spine image by DXA of a 75-80 year-old-woman with thoracic and lumbar scoliosis. VFA was performed using the software programme Physician's Viewer (Hologic).*



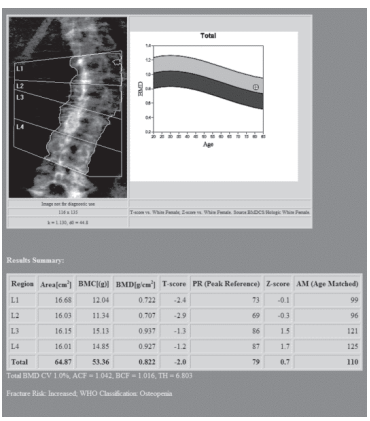


Figure 15 b. *Whole body image*

Figure 15 c. *AP lumbar spine*

1.6 Fracture Liaison Service

A Fracture Liaison Service (FLS) is a fracture prevention programme for secondary prevention.[155] It was introduced to identify patients at risk of fracture and is now spread worldwide.[156] Usually, individuals over the age of 50 presenting with low-trauma fractures (sustained in a fall from a standing height or less) will be contacted for a fracture risk assessment and bone densitometry by DXA and as well as a personalized plan for treatment in order to prevent subsequent fractures. FLSs have been shown to be cost-effective and increase DXA utilization and bone-specific treatment significantly, and also to reduce secondary fractures.[157,158]

1.7 Osteoporosis treatment

Current pharmacological options for osteoporosis treatment include drugs that reduce bone resorption (antiresorptive), drugs that increase bone formation (anabolic), and drugs with dual action.[159,160]

1.7.1 Bisphosphonates

Bisphosphonates (BPs) are the most widely used medication for osteoporosis and have evolved over the last four decades, and today third-generation BPs are used (e.g. oral alendronate, risedronate and intravenous zoledronic acid).[161] BPs have a very high affinity with hydroxyapatite in the bone. During bone remodelling, BPs are resorbed by the osteoclasts, causing an inhibition of the enzyme farnesyl pyrophosphate synthase (FPPS), leading to osteoclast apoptosis and reduced bone resorption.[161] BPs are released from the skeleton for a long time after cessation of treatment due to their long half-life, resulting in persisting effect even during treatment cessation.[162] Circulating BPs are not metabolised and are rapidly eliminated via renal excretion.[161]
When initiating osteoporosis treatment, oral (once weekly; alendronate or risedronate) or intravenous (once yearly; zoledronic acid) BPs are usually the first-in-line treatment in the majority of patients.[163,164] In randomized

controlled trials of postmenopausal women with osteoporosis, BPs reduced the risk of vertebral, nonvertebral and hip fractures by 40-70%, 25-40% and 40-53%, respectively, compared with placebo over three years of treatment.[165-167]

1.7.2 Denosumab

If BPs are contraindicated (e.g. renal failure or hypocalcaemia), not tolerated or if a more potent antiresorptive agent is considered necessary, an appropriate alternative is denosumab (Prolia), a monoclonal antibody to the receptor activator of nuclear factor-kB ligand (RANKL).[168] Denosumab prevents the binding of RANKL to RANK, which results in a strong inhibition of the proliferation and survival of osteoclasts, resulting in a very potent antiresorptive effect. In a randomized placebo-controlled trial in postmenopausal women with osteoporosis, denosumab reduced the relative risk of new radiographic VF, hip and nonvertebral fractures by 68%, 40% and 20%, respectively.[168] Denosumab is administered subcutaneously every sixth month. Compared with BPs, denosumab does not reach a plateau in the BMD increment after 4-5 years, but instead BMD increases continuously with treatment for at least 10 years of treatment.[169] However, denosumab is not incorporated and stored in the bone, resulting in a rapid loss in BMD after with-drawal of treatment, and increased risk of multiple VFs to the approximate level of untreated patients.[170,171] Therefore, to avoid the rebound increase in bone turnover, it is recommended that patients at remaining elevated risk should continue with denosumab or switch to another antiresorptive treatment.

1.7.3 Teriparatide

Endogenous parathyroid hormone (PTH) consists of 84 amino acids and regulates the calcium- and phosphate metabolism in bone and kidneys. Teriparatide (Forsteo) is the active fragment (amino acids 1-34) of endogenous human PTH. It stimulates both bone formation and resorption. However, bone resorption varies according to whether serum levels of PTH are continuously (as seen in primary hyperparathyroidism) or intermittently

elevated. Teriparatide is administered intermittently by daily injections subcutaneously, and has an anabolic effect (preferentially on osteoblasts) on bone formation.[172] In a randomized trial in postmenopausal women with osteoporosis, comparing teriparatide with placebo on new VFs, the relative risk reduction was 65% and absolute risk reduction 9%.[172] In a randomized double-blind trial on postmenopausal women with severe osteoporosis, the effect of teriparatide vs. risedronate on incident radiographic VFs was investigated.[173] At 24 months, 5.4% of women in the teriparatide group and 12.0% of women in the risedronate group had new VFs, corresponding to a relative riskreduction of 56%. Due to high cost, the use of teriparatide has been restricted to patients with prevalent VFs and very high fracture risk.[164,174] Two teriparatide biosimilars (Movymia and Terrosa) were authorized in 2017 by The European Medicines Agency, which has lowered the cost for teriparatide treatment considerably.

1.7.4 Romosozumab

Sclerostin is a protein produced primarily by osteocytes that has anti-anabolic effects on bone formation. Romosozumab (Evenity) is a monoclonal antibody that binds to sclerostin and prevents it from inhibiting osteoblastic activity and bone formation.[30] After the initiation of treatment, bone formation markers increase, but bone resorption markers also decrease due to inhibition of RANKL release from the osteocytes, resulting in the dual action of romosozumab, which acts on both stimulation of bone formation and inhibition of bone resorption.[175] Romosozumab is administered subcutaneously once monthly. In a randomized, double-blind and placebo-controlled trial in postmenopausal women with osteoporosis, romosozumab reduced the relative risk for new VFs by 73% at 12 months. However, a significant risk reduction for nonvertebral fractures was not statistically significant (HR 0.75; 95% CI 0.53 to 1.05, p= 0.10).[176] In a multicentre, double-blind, randomized trial in women with postmenopausal osteoporosis, the effectiveness of sequential treatment was investigated.[177] Women were randomized to romosozumab or alendronate for 12 months, followed by alendronate (open-label) in both groups. The risk of

new VFs was 48% lower in women who were given romosozumab compared with alendronate at 24 months.

1.7.5 Sequential treatment

The anabolic treatment with teriparatide or romosozumab is reversible. To prevent loss in BMD when anabolic treatment is discontinued, an antiresorptive agent should be started, which is known as sequential treatment. The order of medications in sequential treatment is important. If an anabolic agent is started after antiresorptive treatment has "failed", the BMD increase will be blunted as compared to "treatment-naïve" individuals.[178] In a study evaluating bone loss 1 year following 24 months of teriparatide treatment, the LS BMD and FN BMD decreased by 7% and 3%, respectively, in postmenopausal women.[179] Even though BMD remained higher than before treatment start, the bone loss rate was similar to healthy postmenopausal women.[180] In randomized and placebo-controlled studies evaluating the effects on BMD if romosozumab is followed by denosumab [176] or alendronate [177] or abaloparatide (PTH-analog) is followed by alendronate, [181] all studies showed a continuing increase in LS BMD and TH BMD during the treatment period, as well as continued reduced fracture risk. In contrast, switching therapy from denosumab to teriparatide resulted in a transient bone loss at the hip and spine the following year.[182] The current recommendation regarding patients with very high fracture risk and/or severe osteoporosis is to start with anabolic followed by antiresorptive treatment.[159,183]

1.7.6 Calcium and vitamin D

In men and women > 50 years of age, the recommended nutrient intakes of calcium and vitamin D are 800-1000 mg and 800 IU per day, respectively.[164] In randomized controlled trials showing the effectiveness of bone-specific treatment, in most cases calcium and vitamin D supplements were also administered. Therefore, it is recommended that individuals on pharmacological osteoporosis treatment should also receive a daily dose of 500-1200 mg calcium and 400-800 IU vitamin D.[184] Supplementation

with calcium and vitamin D in the absence of osteoporosis medication is not recommended, only to those with ascertained insufficiency of calcium and vitamin D.[184]

1.8 Physical function tests

Physical functioning is an important parameter to assess in the clinical evaluation of older people. The concept of Activities of Daily Living (ADL) was introduced in the 1960s and at that time and the coming decades physical functioning was assessed through self-reported measurements.[185] However, using self-reported measurements, the answers may be influenced by impaired cognitive function, culture, language and education.
During the 1990s, performance-based measurements were introduced as a complement to self-reported measurements.[186] Individuals perform specific tasks in front of an observer, and the results are evaluated according to standardized criteria, resulting in measurements with better reliability and sensitivity to change and more useful as end-points in intervention studies and as prediction for health outcomes.[186] The one leg standing test (OLS) [187], timed up and go (TUG) [188], and 30 sec chair stand test [189], are validated tests for the assessment of balance, mobility, and lower body strength, respectively. Gait velocity may predict adverse events in older individuals [190] and several studies have shown the value of grip strength in predicting important health-related outcomes such as disability, complications, increased length of stay and mortality.[191] Due to differences in how the OLS test is carried out, it has been challenging to obtain a reference value.[192] In a meta-analysis with twenty-one studies included, it was concluded that the average time for TUG for 70 to 79 year olds (men and women) was 9.2 seconds (95% CI: 8.2-10.2).[193] In a meta-analysis with three studies included the reference value for 30 s chair stand test in healthy older Japanese people (men and women) was 17.3 times (95% CI: 16–18.6) but when age was taken into account the reference value for 70 year olds was 18.5 times (95% CI: 9.4–27.6) and for 80 year olds 14.8 times (95% CI: 4.4-25.2).[194] In a systematic review investigating 108 studies on walking tests, it was found that there is great variation between studies regarding

methodology, including how to measure pace and the distance used, which makes comparison difficult.[195]

2. Aims

The overall aim of the thesis was to define the clinical relevance of diagnosing VFs using VFA in older women.

The specific aims of each study were the following:

- To investigate whether or not VFA-identified VFs are associated with bone microarchitecture, bone geometry and density parameters (Paper I).
- To evaluate whether or not VFA-identified VFs are associated with physical function and quality of life in older women, and to study whether mild VFs are clinically relevant as indicated by association with physical function and quality of life (Paper II).
- To determine whether or not grade I VFs are associated with incident fracture in older women, independently of CRFs and BMD (Paper III).
- To examine to what extent VFA-identified VFs improve fracture risk prediction and affect fracture probabilities, independently of BMD and CRFs used in FRAX (Paper IV).

3. Subjects and Methods

3.1 Subjects

All four papers included in this thesis are based on the **S**ahlgrenska **U**niversity Hospital **P**rospective **E**valuation of **R**isk of **B**one Fractures (SUPERB) study. The SUPERB study is a prospective cross-sectional population-based study with the overall aim to identify predictors for fractures in older women. 6,832 women aged 75 to 80, living in the area of Gothenburg, were randomly invited to participate via the Swedish National Population Register between March 2013 to May 2016. They were contacted by letter and thereafter by telephone. Due to exclusion criteria (bilateral hip replacements, not understanding Swedish, not being able to walk with or without a walking aid), 436 (6.4%) were excluded. Out of the 6,396 women who met the inclusion criteria, 3,368 (52.7%) declined to participate, which resulted in 3,028 women being included in the SUPERB study (inclusion rate 47.3%) (**Figure 16**). Data collection took place at the Osteoporosis Research Center, Department of Geriatric Medicine at the Sahlgrenska University Hospital in Mölndal, Sweden.

Papers I and II
At the time of working on Papers I and II, an initial sample of 1,053 women had their lateral spine image analyzed by VFA (**Figure 17**). Of those, 26 women were excluded due to non-analyzable lateral spine images from DXA (extreme scoliosis n=20, inadequate image quality n=4, and extremely high BMI (>40 kg/m2) n=2). In total, 1027 women were finally included in these studies.
In Paper I, a subsample of 472 women were contacted and invited to undergo bone microindentation of the tibia.

Paper III
Out of 3,028 women in the SUPERB cohort, 105 could not be included due to poor image quality of the lateral spine image (n=90) or inability to undergo a lateral spine scan (n=15). 730 women without VFA-identified VF but with self-reported prior fracture, 5 women with information lacking

about self-reported prior fracture, and 93 women who had a combination of grade 1 VF with grade 2 VF and/or grade 3 VF were also excluded. Finally, 2,095 women were included in Paper III. The women were followed from the baseline exam until 24 May 2018.

Paper IV

The same women as in Paper III were initially also included in Paper IV. In this study, the 10-year probability for MOF was calculated using the FRAX methodology. Some women did not answer all the questions regarding CRFs used in FRAX and were therefore excluded (n=70). One woman was excluded due to missing serial number from the Swedish National Board of Health and Welfare, resulting in 2,852 women finally being included in Paper IV. The women were followed from the baseline exam until 31 Dec 2019.

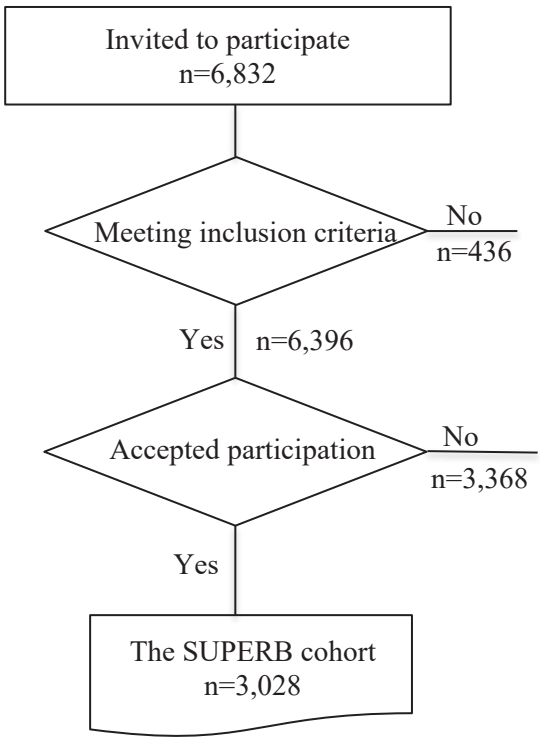


Figure 16. *Flow chart of inclusion and exclusion of the SUPERB study.*

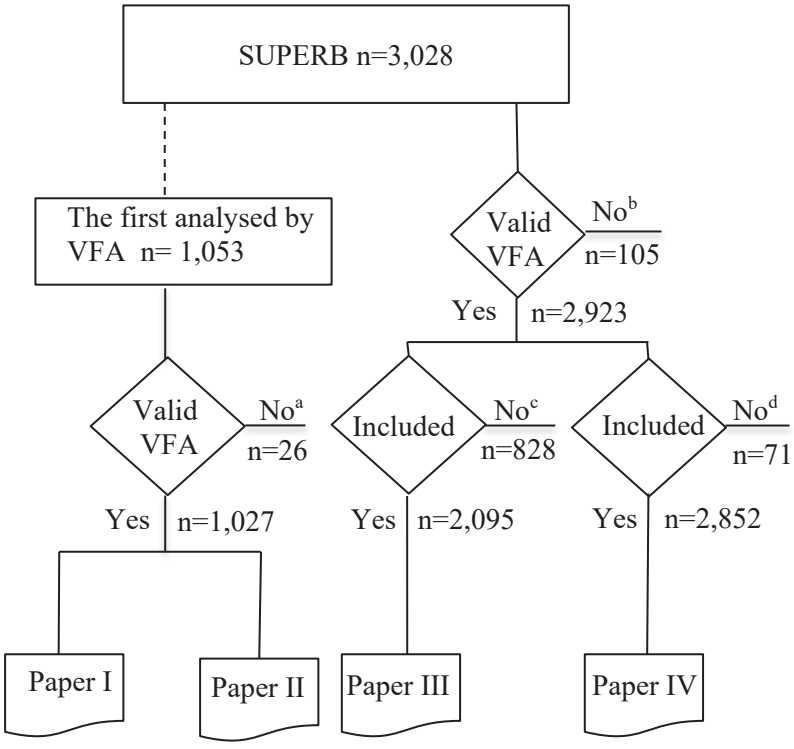


Figure 17. *Flow chart of inclusion and exclusion in Papers I-IV. a=excluded due to poor image quality (e.g. extreme scoliosis, extremely high BMI). b=excluded due to poor image quality (n=90), not able to undergo a lateral spine scan (n=15). c=excluded if no VF but self-reported prior fracture (n=730), information lacking about self-reported prior fracture (n=5) or if grade 1 VF was in combination with grade 2 and/or grade 3 VF (n=93). d=excluded if any answer regarding CRFs was lacking (n=70), did not receive a serial number from the National Board of Health and Welfare (n=1).*

3.2 Anthropometrics

With a standardized, wall-mounted stadiometer, height was measured twice in all 3,028 women. A third measurement was taken if the height differed more than 5 mm. An average of the two most similar measurements was used. Weight was measured to the nearest 0.1 kilogram (**Table 1,** page 54).

3.3 Questionnaires

The international MrOS questionnaire [196] has been used in the Swedish cohort of MrOs.[197] The same questionnaire, with a few modifications, was used for the SUPERB cohort. At baseline, all participants completed a self-administered questionnaire regarding medical history (has a doctor told you that you have osteoporosis, diabetes, hyperthyroidism, rheumatoid arthritis, hypertension, stroke, myocardial infarction, angina, chronic heart failure, chronic liver or kidney disease, cancer, glaucoma, cataract, inflammatory bowel disease, chronic obstructive pulmonary disease), medications (glucocorticoid usage was defined as daily oral treatment with at least 5 mg for a total of 3 months or more), fracture history (skeletal site and time of fracture were asked for, and only fractures sustained after the age of 50 were included in the analyses), parental history of hip fracture, back pain the past 12 months (yes/no), alcohol consumption (excessive intake was defined as consuming more than three standard drinks per day), and current smoking habits. A validated questionnaire was used to estimate daily calcium intake from food and supplements.[198] Current physical activity, for the 7 days prior to assessment was quantified by the validated self-administered questionnaire, the Physical Activity Scale for Elderly (PASE), constructed for individuals over 65 years old.[199] The participants estimated the time (seldom: 1-2 days, sometimes: 3-4 days or often: 5-7 days), and duration (< 1 h, 1-2 h, 2-4 or > 4 h) spent doing different sports or leisure activities, recreation, housework and gardening. A total score was computed by multiplying the amount of time spent on each activity (hours per week) or participation (yes/no) in an activity by empirically derived weights and summarized.

HRQL was assessed using the 12-item Short Form Health Survey (SF-12), a shorter survey developed from the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).[200] It consists of 12 questions of which six items from the scales physical functioning, role-physical, bodily pain and general health provide a value for physical health (Physical Component Summary, PCS), and six items from the scales vitality, social functioning, role-emotional and mental health provide a value for mental health (Mental Component Summary, MCS). The score is weighted and summed

up, and scores range between 0 (the lowest level of health) to 100 (the highest level of health).

3.4 Bone measurements

3.4.1 Dual-energy x-ray absorptiometry

The same DXA device (Discovery A S/N 86491; Hologic, Waltham, MA, USA) was used for most participants (n= 2995). Due to a machine failure 33 women were examined with a Hologic QDR 4500/A Delphi DXA (Waltham, MA, USA). The cross-calibration between the two maschines has been reported in a previous study.[25] Areal BMD (g/cm^2) was measured at the total hip (TH), femoral neck (FN) and lumbar spine L_1 to L_4 (LS), and trabecular bone score (TBS) was measured from L_1 to L_4. If vertebrae at the LS were fractured and/or contained osteosynthesis materials, they were excluded. Areal BMD and TBS at the LS were calculated as the mean of at least two assessable vertebrae. The coefficients of variation (CV) were calculated using duplicate measurements on 30 women. CVs for aBMD of TH, FN, LS and TBS were 0.8%, 1.3%, 0.7% and 2.12%, respectively.

3.4.1.1 Trabecular bone score

In the SUPERB cohort, TBS was calculated as the mean of L_1 to L_4, and fractured vertebrae were excluded. The CV for the method was 1.8% in Paper I (calculated by two repeated measurements on eight women), and 2.1% in Paper III (calculated by two repeated measurements on 30 women).

3.4.2 High-resolution peripheral quantitative computed tomography

In the SUPERB cohort, all participants' distal radius and distal tibia (non-dominant side, in case of prior fracture, the other side was used) were measured using a HR-pQCT device (XtremeCT; Scanco Medical AG, Brüttisellen, Switzerland) (**Figure 18**). A reference line is manually placed

at the articular surface of distal radius and distal tibia. Proximal from this line, at a distance of 9.5 mm at radius and 22.5 mm at tibia, the first CT slice is acquired and followed by another 109 slices, yielding the measurement cylinder, labeled the standard (or ultradistal) site.[72,201] A more proximal site (at 14% of the bone length from the reference line) was used to measure cortical bone, labelled the distal site.[202] At each scan site, 110 parallel cross-sectional images were obtained, reproducing a 9.02 mm 3D image of the bone. As recommended by the manufacturer, the quality of the images was graded from 1 to 5. Only images with acceptable quality, 1 to 3, were used in the analyses. To separate the extra-osseal soft tissue from the periosteal surface, a contour was automatically placed around the bone, and operator-corrected if needed. Parameters obtained were: trabecular bone volume fraction (BV/TV, %), trabecular number (mm^{-1}), trabecular thickness (mm), trabecular separation (mm), cortical volumetric BMD (mg/cm^3), cortical area (mm^2), and total volumetric BMD (mg/cm^3).

To obtain CVs, measurements on 30 women were made. The CVs for measurement of trabecular parameters in the distal radius and distal tibia were 0.4% to 2.5% and 0.8% to 2.6%, respectively. CVs for the measurement of cortical parameters in the distal radius and distal tibia were 0.1% to 0.9%.

With software (Image Processing Language; IPL v5.08b) from the manufacturer (Scanco Medical AG), the cortical bone was separated from the trabecular bone by automatically placed contours at the endosteal surfaces of the bone, which could be corrected by the operator if needed. From this image, the cortical parameters measured were: cortical pore volume (Ct.Po.V; mm^3), cortical bone volume (Ct.BV; mm^3), and cortical porosity (Ct.Po; %), which was calculated as Ct.Po.V/(Ct.Po.V+Ct.BV).[203] CVs for measurement of cortical porosity at the distal radius and distal tibia were 5.3% to 13.3% and 0.9% to 4.1%, respectively.

***Figure 18**. XtremeCT; Scanco Medical AG, Brüttisellen, Switzerland*

3.4.3 Bone microindentation

In Paper I, a subsample of 472 women from the SUPERB cohort underwent bone microindentation of the tibia. To calculate BMSi, RPI was performed with an Osteoprobe device (Active Life Scientific, Santa Barbara, CA, USA) as described elsewhere.[202,204]

Local anaesthesia was administered on the midshaft of the anterior tibia and the needle of the Osteoprobe was inserted through the skin and periosteum. With a preload of 10 N the probe was established on the bone, and thereafter by a trigger mechanism further inserted with an impact force of 30 N, which takes less than a millisecond, creating a small microfracture, 375 µm across (**Figure 19 a-c**).[77] The distance the probe moves into the cortical bone from the established position is called the indentation distance increase (IDI). At least 11 valid indentations were performed on each participant. Five indentations were then made in a polymethylmethacrylate

plastic calibration phantom. The BMSi for each participant was calculated as the ratio between the mean of the five indentations in the plastic phantom, divided by the IDI into the bone, and multiplied by 100. A deeper cavity results in a lower BMSi, indicating a lower bone material strength. BMSi was assessed by four different operators and possible differences between operators were investigated with interobserver CV, which was 5.2%. The intraobserver CV for BMSi in elderly women was 3.2%.[202]

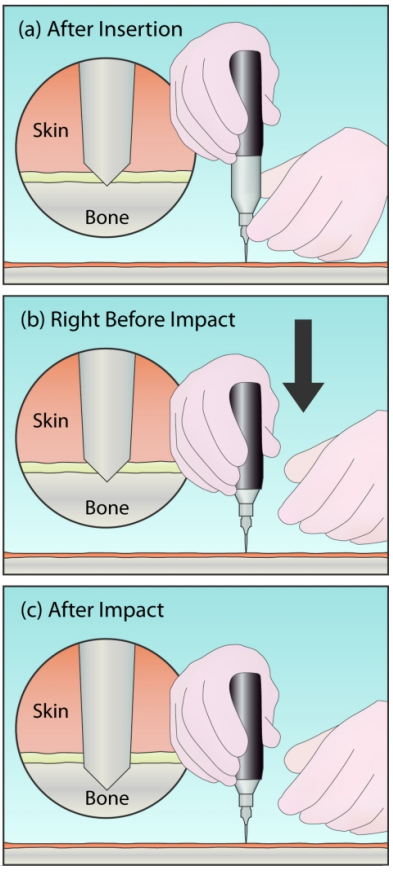


Figure 19 a-c. *Bone microindentation by using Osteoprobe. Reproduced from [77],* ***with the permission of AIP Publishing.***

3.5 Physical function tests

3.5.1 One Leg Standing (OLS)

OLS tests balance. Women were asked to choose which leg they preferred to start with, and with eyes open and arms across the chest, to lift their foot from the ground with flexed knee (**Figure 20**) for as long as they could manage, while being timed.[187] The timing was stopped when the foot touched the ground again, if the weight-bearing limb moved, if the arms moved from the chest, or when the timing reached 30 s. The test was performed twice, and in the analysis, the maximum value was used.

Figure 20. *Illustration of the One Leg Standing test (OLS)*

3.5.2 Timed Up and Go (TUG)

Women's mobility and balance were tested by measuring the time in seconds it took to rise from a chair, walk three metres at normal pace, turn around, walk back and then sit down again (**Figure 21**).[188] Participants were allowed to wear footwear of their own choice and use walking aids if

needed. The chair was 45 cm high with armrests. The test was repeated once with a glass of water in one hand.

Figure 21. *Illustration of the Timed Up and Go (TUG)*

3.5.3 30 s Chair Stand Test

This test measures lower body strength.[189] From sitting position on a chair without armrests, with arms across the chest, the participant on the command "go" rises to standing position and then sits down again and repeat this as many times as possible in 30 s (**Figure 22**).

Figure 22. *Illustration of 30 s Chair Stand Test*

3.5.4 Walking speed

Gait velocity is a measurement that can predict adverse events in healthy older people.[190] With the timed 10-m walking test, each participant walked 10 m at a pace they found comfortable. Time-keeping started after 2 m and ended at 8 m to exclude the time for acceleration and deceleration (**Figure 23**).[205] The mean value of two repeated tests was recorded in metres per second.

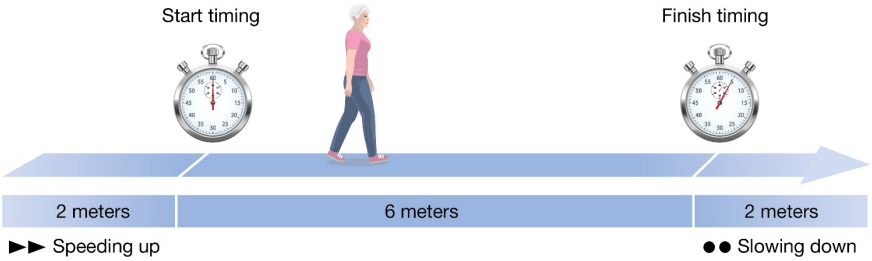


Figure 23. *Illustration of walking speed*

3.5.5 Grip strength

A Saehan hydraulic hand dynamometer (model SH5001; Saehan Corporation, Masan, Korea) was used to measure the grip strength in the dominant hand. With the elbow flexed at 90° and the arm resting on a table, two attempts were made (**Figure 24**). The average strength, measured in kilogrammes, was used in the analyses.[206]

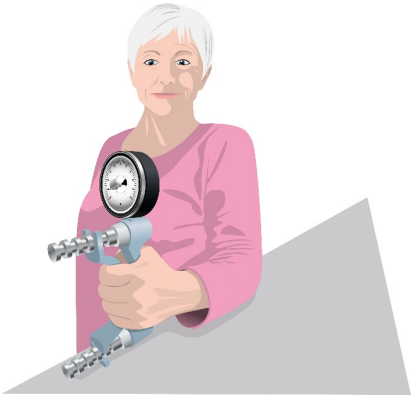


Figure 24. *Illustration of grip strength testing.*

3.6 Fractures

3.6.1 Prevalent self-reported fractures

Information regarding previous fractures was collected by a self-administered questionnaire at baseline. Data was collected both on the localization of the fracture and at what age it happened. Fractures of the skull, hand and foot were excluded, and only fractures after the age of 50 were used in the analyses. Severity of trauma was not considered. Studies have shown that BMD is reduced in patients with both high and low trauma fractures [4] and that high trauma fractures are also associated with subsequent incident MOF.[5,207]

3.6.2 Prevalent vertebral fractures by VFA

In conjunction with the DXA exam (Discovery; Hologic) at baseline, a lateral spine image was taken with the participant in supine position. The fourth lumbar vertebra was marked by the DXA operator after looking at the AP image of the lumbar spine. The images were then analyzed using the software programme Physician's Viewer (Hologic) described in chapter 1.5.3.

In Papers I and II**,** the VFA analyses of all 1,027 subjects were carried out by one examiner (LJ). The reproducibility was tested on 50 women (T_4 to L_4) and the intraobserver agreement was 98.9% (kappa score 0.85). The interobserver agreement between LJ and HB (co-author Paper I) was 97.6 % (kappa score 0.72). When mild vertebral fractures were excluded, the intraobserver agreement was 100% (kappa score 1.0) and the interobserver agreement 99.6% (kappa score 0.95).

In Papers III and IV, the VFA analyses of all 3,028 subjects were carried out by two examiners, of whom LJ analyzed two-thirds and KR (co-author Paper III) analyzed one-third of all scans. The intraobserver agreements for the two examiners were 98.9% and 97.8%, and kappa scores were 0.85 and 0.67, respectively. When separating grade 1 VFs from grade 2–3 VFs, the

interobserver agreement and kappa score for grade 1 was 99.1% and 0.66, and for grade 2–3 99.4% and 0.84.

3.6.3 Incident fractures

Incident fractures were collected in two ways.
In Paper III, incident fractures were x-ray verified between the baseline exam until 24 May 2018. All the radiology reports and/or images from a regional digital x-ray archive, including 49 municipalities covering an area of 25,000 square kilometres surrounding Gothenburg, were reviewed by three research nurses, and all reported fractures were noted. If there were any doubts about fracture diagnosis or if radiology reports were missing, images were reviewed by an orthopaedic surgeon (LJ).
In Paper IV, the aforementioned x-ray-verified fractures were supplemented with data on incident fractures from the National Patient Register (NPR) administered by the Swedish Board of Health and Welfare. Incident fractures were collected by using the International Classification of Diseases, 10th Revision (ICD-10) codes from baseline until the 31 December 2019.[208,209]

3.7 Fracture Risk Assessment Tool (FRAX®)

In Paper IV, the 10-year probabilities for hip fracture and MOF, with or without BMD, were calculated at baseline for the 2,852 individuals from the SUPERB cohort who had answered all the questions regarding CRFs used in FRAX. Hazard functions for fracture and death were computed for 10-year probabilities of MOF with or without BMD, and significant interactions for each risk factor, determined from meta-analyses, were entered in the models.

Methods used	P- I	P-II	P-III	P-IV
Anthropometrics	x	x	x	x
Questionnaires	x	x	x	x
DXA	x	x	x	x
TBS	x		x	
HRpQCT	x			
Bone microindentation	x			
OLS, TUG, 30 s chair stand test, walking speed, grip strength		x		
VFA	x	x	x	x
Incident fractures			x	x
FRAX				x

Table 1. *Methods used in the different Papers (P)*

3.8 Ethics

Ethical considerations in Papers I-IV are mainly the exposure to radiation and infringement of participants' personal integrity, especially for Papers III-IV due to data collection on incident fractures. Radiation exposure of a DXA scan of hip and spine (1-10 µSv) including VFA (3 µSv) and HRpQCT of distal radius and distal tibia (< 5 µSv) is considered a low dose of radiation, and does not exceed an approximate 2 days of natural background radiation (5-10 µSv per day).[52] The radiation exposure was approved by the local radiation protection committee. Other ethical considerations for Paper I are the blood sampling and the bone microindentation measurements, which are invasive procedures although serious

complications are very rare. Regarding personal integrity, data was collected and recorded in a coded form and the results are anonymized and presented at a group level only. All the participants were informed orally and in writing that they could withdraw their participation and consent at any time without any further explanation. All the study participants gave their informed consent and the study and study amendments were approved by the Ethical Review Board in Gothenburg (Dnr. 929-12).

3.9 Statistics

The independent samples *t* test was used for comparing means between two independent groups for continuous variables if normally distributed. For categorical variables, the Chi-square test was used. Fisher's exact test was used if the number of categorical variables was small. When comparing means for continuous variables between more than two groups, one-way analysis of variance (ANOVA) was used, followed by the least significant difference (LSD) post hoc test in Papers I-II, or by the Bonferroni post hoc test in Papers III-IV (**Table 2,** page 60). The results were presented as mean value ± SD. To assess whether associations were still valid after adjustment with covariates, multivariable logistic regression analyses were performed when the outcome (dependent variable) was dichotomous, and multivariable linear regression was used for continuous outcomes. The results were presented as odds ratios (OR) with 95% CI per SD change in each variable and standardized β coefficient and p-value. In Papers III and IV, the incidence per 1000 person-years was calculated as number of events divided by total follow-up time (until fracture, death, or censored) per 1000 years, and post hoc statistical power analyses were performed.
P-values less than 0.05 were considered significant. All statistical analyses were performed with SPSS Statistics Version 21 in Paper I and Version 25 in Papers II-IV (IBM Corporation, Armonk, NY, USA).

3.9.1 Survival analysis

A survival analysis measures the time in a sample of individuals until a specific event occurs ("time to event analysis"). Another characteristic of survival analysis is that not everyone will experience the event. Reasons may be that the study ends before event occurs, study subjects move to another country or they die (lost to follow-up), and these are censored observations, although they are not "missing observations". Survival analysis was originally developed for mortality studies but can be used for different outcomes, e.g. fracture outcomes as in Papers III and IV. There are different kinds of survival analysis. A Kaplan-Meier curve estimates the proportion of survival at each point in time. It is a descriptive method and does not allow consideration of covariates. The log-rank test is similar to the Kaplan-Meier curve but for two or more groups. It provides a p-value and assesses whether curves differ significantly. It does not consider covariates or interactions. An interaction occurs when a variable has an effect on the outcome depending on the values of another variable.

Cox regression proportional hazards model

The Cox regression proportional hazards model is a survival analysis which takes covariates and interactions into account, but some assumptions have to be fulfilled for this model to work. The most important assumption is that the ratio of the hazards for any two groups is constant over time, i.e. they are proportional. This can be tested in different ways, e.g. Schoenfeld plot, Cox with time-dependent variable, or log-minus log plots. In Paper III, Cox models with time-dependent covariates were used to ensure that interaction term between time and VF was not significant, and log minus log plots were used to ensure parallel lines visually, indicating proportionality between the groups, which was tested on each outcome (any fracture, MOF and VF). Another assumption is that the survival times (t) are independent, i.e. the survival time of one individual is independent of the survival time of another individual. The outcome has to be dichotomous, e.g. fracture or no fracture. In Cox regression, it is possible to analyse the cumulative hazard, i.e. the risk of suffering a fracture at time t between time 0 and time t. The survival function at time t is the probability

of not suffering a fracture to time t. Hazard ratios (HR) > 1 indicate an increased risk for the event and a HR < 1 indicates a reduced risk. The HR estimates are given with a CI, which is an estimate of how certain the mean HR value is, and usually a confidence level of 95% is used. Covariates may be time-dependent (i.e. change with time during follow-up) or fixed (e.g. sex, ethnicity).

Modified Poisson regression model

By using Poisson regression, the probability of an outcome (dependent variable) given one or more independent variables (predictors), can be analyzed. The outcome should be "count data", i.e. 0,1,9,13,345 etc. and can not be less than zero. Each observation (e.g. fracture) should be independent of any other observation (in another individual), i.e one observation can not provide any information about another one. The independent variables can be continuous or categorical (ordinal or nominal/dichotomous). If the observations follow a Poisson distribution, it means that the expected and observed observations are similar, the model predicts the observed observations well. However, in Paper IV, a modified Poisson regression model was used for examining the association between VFA-identified VF and the risk of fracture with adjustments. In this modified Poisson regression, the time t (observation time) is divided into small time periods of one month, providing a dichotomous outcome as in Cox (the probability for more than one event per month is very low), resulting in an instantaneous hazard function. The HR is the instantaneous risk (at any time during the follow-up) for either suffering a fracture or not. For fracture, the variables in the hazard function were current time since baseline, current age, BMI, previous fracture, family history of hip fracture, smoking, corticosteroids, rheumatoid arthritis, alcohol use, secondary osteoporosis, and BMD. One additional model was constructed using the variables mentioned above and adding VFA. Hazard functions are based on the approximately 5 years of follow-up time, and then extrapolated in time providing the 10-year probability, which is an estimation, beyond the original observation range, but based on the relationship with the other variables. When studying probabilities of fracture for populations with more advanced ages it is important

to take into account the competing risk of death. When the 10-year probability of MOF was calculated, using hazard function of fracture, the hazard function of death was also calculated and included in the calculation. For death, the variables in the hazard function were current time since baseline, current age, BMI, current smoking, per oral corticosteroid use, and BMD. As an example, the 10-year probabilities of MOF for women 75 and 80 years old, with previous fracture, were calculated, setting BMI to 26 kg/m^2, but no other CRFs, according to FN BMD T-score, with VFA-identified VF and without considering VFA in the analyses.

3.9.2 Multivariable adjustment

Regression analyses (linear, logistic, Cox or Poisson) were performed in all four papers. By using multivariable adjustment, the relative contribution of other explanatory variables for the outcome can be examined. Depending on which and how many variables are entered into the model, the conclusions may differ. Overfitting is when too many variables are included relative to the lower number of individuals or outcomes, and may confuse conclusions. Our intention was to include an adequate number of explanatory variables (also called risk factors or independent variables) based on previous knowledge (studied or a priori) of what might influence the outcome, although results may be confounded by unknown or unmeasured variables.[210] In Papers III–IV, multivariable analyses were performed in three steps with increasing numbers of covariates.

3.9.3 Intra-rater and inter-rater reliability and kappa statistics

The simplest form of intra- and inter-rater reliability is percent agreement, i.e. the proportion of agreement of measured value between two independent assessors. It is best suited for a nominal measurement level.[211] However, there may be a possibility that the raters may not know how to measure, and so guess randomly. Then an agreement will be a false agreement and due to chance instead. To account for this, Jacob Cohen introduced Cohen's kappa in 1960. The kappa coefficient can range from -1 to

+1, where 1 represents perfect agreement between the raters. Values below zero are possible but unlikely. The formula is: (observed agreement – chance agreement) / (1-chance agreement). The kappa result may be interpreted as: values ≤ 0 as indicating no agreement and 0.01–0.20 as none to slight, 0.21–0.40 as fair, 0.41– 0.60 as moderate, 0.61–0.80 as substantial, and 0.81–1.00 as almost perfect agreement. However, a limitation of Cohen's kappa is that it is not easy to interpret depending on the context, and also it may lower the agreement too much, while percent agreement may give a falsely high agreement. The recommendation is to use both the percent agreement and the kappa statistics.

3.9.4 Coefficient of variation

The coefficient of variation (CV) is used to measure the dispersion of data around the mean. SD is also a measure of the dispersion of data but comparing two samples with different SD's may be inappropriate if different scales are used. Small numbers will result in low SDs and high numbers in high SDs, even if they are equal in percentages. CV is the ratio of the SD to the mean. When CV is expressed in percentage, SDs on different scales may be compared. CVs of 5% or less are considered good, whereas CVs of 10% or more are considered inadequate.

Statistical methods used	P- I	P-II	P-III	P-IV
Independent samples t test	x	x	x	x
Chi-square test	x	x	x	x
Cohen's kappa	x	x	x	x
Coefficient of variation	x	x	x	x
Fisher's exact test			x	x
ANOVA and *post hoc* test	x	x	x	x
Multivariable logistic regression	x	x		
Multivariable linear regression		x		
Cox proportional hazard models			x	
Poisson regression (modified)				x

Table 2. *Statistical methods used in the different Papers (P)*

4. Results

4.1 Paper I

The prevalence of vertebral fractures is associated with reduced hip bone density and inferior peripheral appendicular volumetric bone density and structure in older women

In the first study, we investigated whether prevalent VF, verified by VFA, was associated with bone microarchitecture parameters and bone material strength in older women.
In the cohort of 1,027 women from the SUPERB study, bone microindentation was performed on 472 women.

4.1.1. Main results

Of 1,027 women, 750 (73%) were non-fracture subjects and 277 (27%) had at least one VF. There was no difference in age between women with and without fracture (77.8±1.4 and 77.7±1.6, (mean±SD) respectively). Of the 277 women with VF, 107, 107 and 63 had mild, moderate or severe VF, respectively. The women with VF were also divided into having only one VF (n=194), two VFs (n=56), or more than two VFs (n=27).

Women with VFA-identified VF

- were shorter, had more self-reported fractures after 50 years of age and used osteoporosis medication more often than women without VF.
- had significantly lower aBMD of the FN, TH, LS and lower TBS compared with women without VF.
- had significantly lower aBMD of the TH also when VFs were divided into number and severity, compared with women without VF.

- did not have significantly different BMSi, measured with RPI, compared with women without VF.
- had significantly lower trabecular BV/TV at both distal radius and distal tibia compared with women without VF.
- did not have significantly different cortical bone parameters compared with women without VF, except for cortical bone area at the distal tibia.

In a subanalysis, only TH aBMD remained independently associated with VF when either TBS, cortical area or trabecular bone BV/TV was included in the logistic regression with covariates.

4.1.2. Conclusion

In this population-based cohort of older women, TH aBMD was consistently independently associated with the presence of a VFA-identified VF. Parameters reflecting cortical strength as BMSi and cortical porosity, were not associated with VF, indicating that cortical bone traits are of minor importance in women with VFs.

4.2 Paper II

Vertebral fractures and their association with health-related quality of life, back pain and physical function in older women

In this study, the women included were the same as in Paper I. Of the 1,027 women, 277 (27%) had at least one VF. We investigated whether VFA-identified VFs were associated with HRQL, back pain and physical function. Physical function was tested using performance-based measurements (OLS, TUG, 30-s chair stand test, walking speed and hand-grip strength). The purpose was also to investigate whether mild VFs were associated with these parameters.

4.2.1 Main results

Of 277 women with at least one VF, 107 had only mild VF.

Women with VFA-identified VF

- had worse physical health than women without VF.
- had similar mental health compared with women without VF.
- had more frequent back pain than women without VF.
- had worse physical function than women without VF.
- had similar grip strength as women without VF.

Using linear regression models with covariates (age, weight, height, fall accident last year, Parkinson's disease, rheumatoid arthritis, stroke, hypothyroidism, hypertension, cataract, cancer, asthma/bronchitis/emphysema, diabetes, smoking, alcohol, scoliosis, self-reported fracture), it was evident that prevalent VF was independently associated with physical health in all groups of VFs (any, number and severity). Regarding physical function, TUG, walking speed and 30-s chair stand test were independently associated with prevalent VF in all groups (except 30-s chair stand test and number of VFs), calculated by using linear regression models with covariates (age, weight, height, fall accident last year, PASE, Parkinson's disease, rheumatoid arthritis, stroke, hypothyroidism, hypertension, cataract, cancer, asthma/bronchitis/emphysema, diabetes, smoking, alcohol, scoliosis). Using logistic regression models with covariates (age, weight, height, fall accident last year, Parkinson's disease, rheumatoid arthritis, stroke, hypothyroidism, cataract, cancer, smoking, alcohol, self-reported fracture, scoliosis), we found that all three groups of prevalent VFs were independently associated with back pain.

Women with mild VFA-identified VF

- had worse physical health (PCS) and physical function (OLS and 30-s chair stand test) than women without VF (unadjusted).

4.2.2. Conclusion

The performance-based physical function tests TUG, walking speed and 30-s chair stand test, physical health investigated by SF-12, and back pain were independently associated with prevalent VFA-identified VF. Also, mild VFs were associated with worse physical function and physical health. These findings indicate the usefulness of VFA in diagnosing clinically relevant VFs.

4.3 Paper III

Grade 1 vertebral fractures identified by densitometric lateral spine imaging predict incident major osteoporotic fracture independently of clinical risk factors and bone mineral density in older women.

2,095 women from the SUPERB study were included in this study. We investigated whether grade 1 (mild) VFA-identified VFs were associated with incident fractures, independently of CRFs and BMD. Incident fractures were x-ray-verified.

4.3.1. Main results

264 women had one or more grade 1 VF, 349 women had a grade 2 and/or a grade 3 VF and 1,482 women did not have any VFA-identified VF or self-reported fracture. The prevalence of grade 1 VF was most frequent at the T7 and T11 level. During a median follow-up time of 3.6 years, 260 women had any incident fracture, 213 and 101 women sustained a MOF (fracture of the proximal humerus, forearm, hip, spine, and pelvis) or VF, respectively.

Women with grade 1 VFA-identified VF

- were older than women without fracture.
- had lower BMD at the FN and LS, and lower TBS than women without fracture.

Using Cox proportional hazard models with adjustments for age, height and weight, women with grade 1 VFA-identified VF had 67% increased risk for suffering any fracture (HR = 1.67; 95% CI 1.18–2.36) and 86% increased risk for MOF (HR = 1.86; 95% CI 1.28–2.72). When CRFs (previous fracture, family history of hip fracture, oral glucocorticoid use, osteoporosis medication, rheumatoid arthritis, current smoking, excessive alcohol intake) and FN BMD were added into the model, the risk for MOF remained significant (HR = 1.72; 95% CI 1.08–2.76).

4.3.2. Conclusions

In this cohort of older women aged 75 to 80, the prevalence of grade 1 VFA-identified VFs increased the risk of suffering a future MOF, and this association was independent of CRFs and BMD. These findings indicate that even mild VFs identified by DXA should be taken into account when evaluating fracture risk in older women.

4.4 Paper IV

Improved fracture risk prediction by adding VFA-identified vertebral fracture data to BMD by DXA and clinical risk factors used in FRAX

Of the 3,028 women in the SUPERB study, 2,852 women had answered all the questions regarding CRFs used in FRAX, and could be included in this study. We investigated what impact VFA-identified VFs had on fracture probability, and whether this impact was independent of CRFs and BMD used in FRAX. We also investigated whether the impact of a VFA-identified VF on fracture probability was beyond the presence of a prior self-reported fracture. Using a modified Poisson regression, the association between a VFA-identified VF (any) and the risk of fracture was calculated. The hazard functions for fracture and death could then be used to extrapolate the follow-up time to 10-years and then calculate the 10-year probability of MOF, both with VFA taken into account and VFA not taken into account. As in Paper III, incident fractures were verified by x-ray until 24 May 2018, but also by diagnosis codes until 31 December 2019.

4.4.1. Main results

2,163 women did not have any VFA-identified VF and the 689 women with a VFA-identified VF were divided into different groups, either any but also into number and severity of VF. 1,805 women did not report a prior fracture, and out of these, 359 (20%) had a VFA-identified VF. The women were followed for 5.2 years (median) and during this time 229 died and 422 women suffered a MOF of which 160 had a clinical VF and 124 a hip fracture.

Women with VFA-identified VF

- were older and shorter and had lower BMD than women without VF.
- had more frequently prior fracture and higher FRAX 10-year probability (at baseline), than women without VF.

The risk of MOF was increased 52% independently of CRFs used in FRAX and BMD, and having 3 or more VFA-identified VFs increased the risk for an incident clinical VF by almost six times. For example, in these models, a 75-year-old woman with a previous self-reported fracture and BMD T-score -2, the 10-year probability of MOF increased from 29.5% (without considering VFA) to 36.7% (having a VFA-identified VF) corresponding to a 1.24-fold increase in the 10-year probability of MOF.

4.4.2 Conclusions

The 10-year probability of MOF increased substantially when VFA-identified VFs (independently of severity), together with FRAX CRFs and BMD were included in the model. This indicates the usefulness of VFA in clinical practice when assessing the fracture risk in older women.

5. Discussion

The general aim of this thesis was to investigate whether VFA, in conjunction with DXA, could be of importance in clinical practice to enhance fracture risk assessment. The reasons for this are several.

The significance of identifying VFs

Women with a prevalent VF have a 4 times greater risk of sustaining a new VF, with the risk increasing with the numbers of preexisting VFs, and almost twice the risk of non-vertebral fractures than women without VF.[20] Since VF is regarded as one of the strongest predictors for subsquent fracture, with osteoporosis medications reducing the risk of new fractures effectively, [159,160] it is of the greatest importance that VFs come to clinical attention. However, the challenge is to find the two-thirds of patients with asymptomatic VFs.[14]

In Paper I, we examined whether prevalent VFs, identified by VFA, were associated with bone traits, assessed by HRpQCT, DXA and BMSi. Previous studies have shown associations between VF and bone microstructure (by HRpQCT). However, these studies were small, case-controlled and VFs were identified by spine x-ray. [212-214] Due to these differences in study design between theirs and ours, the results are not easy to compare. In concordance with our results, in a study of 100 women with VF (identified by spine x-ray), Sornay-Rendu et al. [213] found associations between low vBMD at the radius and tibia (by HR-pQCT) and greater number and severity of VF, independently of age and LS BMD, although in our study we did not adjust for LS BMD but for age, height, weight, family history of hip fracture, treatment with glucocorticoids, treatment with bone active drugs, smoking, alcohol and rheumatoid arthritis. In contrast to our study, they also found alterations of cortical bone at the radius and tibia in women with VF, independently of LS BMD, and these bone traits were even worse due to severity and numbers of VF. Stein et al. [214] also found worse trabecular and cortical microarchitecture in 30 women with VF compared with women without VF (adjustment for radial BMD for radial parameters

or TH BMD for tibial parameters). However, they did not find any associations between the number or severity of VFs and microarchitectural alterations. Nor did they find any differences in BMD (by DXA) at any sites (except ultradistal radius) between groups with and without VF. In our study on the contrary, the strongest predictor for having a VF was TH BMD. When TH BMD was included in logistic regression models with either of the parameters independently associated with a VF – trabecular BV/TV (radius), cortical area (tibia), cortical vBMD (tibia), total vBMD (radius or tibia) or TBS (by DXA) – none of these parameters remained independently associated with VF except TH BMD, which remained independently associated to VF in all these models. In a cohort of 16,505 women 50 years of age or older, Leslie et al. examined which BMD site (by DXA) was most useful for prediction of fracture. [215] They concluded that TH BMD alone was superior the other sites for fracture prediction, although the LS BMD was the most useful site for prediction of VFs alone. In our cohort, LS BMD was not associated with all categories of VF, which could possibly be explained by overestimation of LS BMD due to degenerative changes in this older cohort of women (mean age 78 years vs 65 years). [111] Theoretically, in older women with degenerative changes in the LS, TH BMD would be the site of choice for overall osteoporotic fracture prediction as well as for VFs alone. The rationale for this is the larger amount of trabecular bone in the TH compared with the FN. In our study, we did not find any evidence for inferior cortical bone properties. While TBS, which is a parameter assessing trabecular bone quality by DXA, was independently lower in women with prevalent VFs, neither BMSi (by bone microindentation testing in vivo of cortical bone at tibia), nor cortical porosity (by HR-pQCT) were associated with prevalent VFs in our cohort, indicating an inferior role of cortical bone quality in the pathogenesis of VF. However, others raise the importance of cortical measurements to assess tendency to fracture [213,214,216-219], yielding this as a field for further research.

Another research field to be explored, for which previous studies are lacking, is whether VFA-identified VFs are associated with physical function, assessed by multiple, validated, performance-based measurements.

In Paper II we showed that VFA-identified VFs (using the same cohort as in Paper I) were independently associated with TUG, walking speed and

30-s chair stand test. Morris et al. investigated whether balance tests could predict falls in a cohort of community-dwelling women aged 60 with VFs.[220] They found that the best test to predict falls in older women with VFs was the 5-m-TUG test (we used a 3-m-TUG test). In a recently published study on 3,028 women from the SUPERB cohort, investigating whether TUG time was associated with fracture risk independently of CRFs and BMD, it was found that fracture incidence increased with increasing TUG time up to 12 seconds and thereafter started to level off.[221] The cutoff level for slow TUG time was set to > 12 s and in Cox models the association between slow TUG time and fracture risk was examined. It was concluded that a slow TUG time > 12 s increases the risk of MOF or hip fracture independently of CRFs and FN BMD by 76% (HR 95% CI 1.76 [1.30-2.40]) and 93% (HR 95% CI 1.93 [1.00-3.71]), respectively.[221] These results motivate including the TUG test in clinical practice to improve the risk assessment of fractures and falls. It is an easily accessable test, since nothing else than a chair is needed and the test only takes a minute or two. In another but similar study, OLS was examined in the same SUPERB cohort.[222] A low OLS time < 10 s was associated with MOF and hip fracture independently of CRFs and FN BMD (HR 95% CI 1.58 [1.20-2.08] and HR 95% CI 2.39 [1.17-4.86], respectively). In our study, women with VFA-identified VFs had a significantly lower OLS time compared with women without fracture. If VFs are categorized according to severity, then women with mild VFs also had significantly lower OLS times than controls, although this significance did not remain when adjusted for covariates. Interestingly, when dividing VFs according to severity, physical health, assessed by SF-12, was also significantly inferior in women with mild VFs than in women without fracture (mean±SD 43.8±10.9 and 46.2±10.5, respectively, p value < 0.001), which remained significant after adjustment with multiple covariates. However, a statistically significant difference is not always clinically relevant. There are no previous studies on the minimal clinically important differences (MCID) of PCS in patients with VF, but MCID of PCS in patients with subacute and chronic low back pain was reported to be 3.3 or greater.[223] In Paper II, the difference in PCS between women with mild VF and women without VF was 2.4, although in women having more than two VFs the difference in PCS was 7.2 compared with women without VF.

Mild VFA-identified VFs

Regarding mild VFs, whether or not they are important to identify is still controversial. While some have reported that even mild VFs are associated with impaired HRQoL [99,224] or subsequent fractures, [225,226] most studies so far have either not classified the prevalent VFs according to severity or they have focused on moderate and severe VFs. [20,227,228] Only one study, as far as we know, has examined the role of VFA-identified VFs, according to severity, in predicting future fracture risk, and the predictive value of mild VF could not be verified.[229] To our knowledge, Paper III is the first study to show the predictive value of mild VFA-identified VFs on fracture risk. However, there are some difficulties to consider when identifying mild VFs. Due to poor visualization of the upper thoracic vertebrae, mild VFs can be missed. However, VFs at level T4-T5 are rare and VFA is a reliable method to detect VFs at level T7-L4 compared with conventional x-ray, with an agreement in deformity identification between VFA and x-ray of 96.5% (κ=0.81).[151] While some have questioned the reliability of VFA for detecting mild VFs, [230] others have shown good agreement between VFA, including mild VFs, and spine x-ray (κ=0.74).[231] Depending on which morphometric method is used to identify VFs and how a minor deformity is classified, the prevalence of VFs can range from 3% to 90%.[105,108] In Papers I-IV we have used the GSQ method because it is the most widely used, and with the semi-quantitative approach, other morphologic deformities such as Schmorl's nodes, SVH, Scheuermann's disease, degenerative changes, scoliosis and Cupid's bow deformity can be differentiated from fractures (chapter 1.4.4).[119] To be able to distinguish these differential diagnoses from VFs, some experience and training are required.[232] Mild VFs are important to identify because of the vertebral fracture cascade (Chapter 1.4.3).

The importance of interrupting the vertebral fracture cascade

To prevent subsequent fractures, the vertebral fracture cascade has to be interrupted. Firstly, all VFs (symptomatic as well as asymptomatic) have to be detected by spinal imaging. According to the ISCD, spine imaging

(by standard radiography or VFA) is recommended when the T-score is less than -1.0 and one or more of the following conditions is present: women aged ≥70 and men aged ≥80, historical height loss >4 cm, self-reported prior VF, glucocorticoid therapy ≥5 mg of prednisolone or equivalent per day for ≥3 months.[233] Secondly, if a VF is detected, the vertebral fracture cascade can effectively be interrupted by osteoporosis medication, and treatment should, if appropriate, commence as soon as possible after the fracture according to treatment guidelines.[164] However, VFA is not used enough globally even though secondary prevention programmes such as FLSs are increasing worldwide.[234] In a non-FLS clinical setting, prevalent VFs by VFA increased the number of patients eligible for osteoporosis treatment by 35% compared with not knowing VFA results [235] and from a FLS in the United Kingdom, 25% of patients presenting with a non-hip, nonvertebral fracture had an undiagnosed VF.[236] This finding is in concordance with our results in Paper IV, even though ours is a population-based study, in which VFA-identified VFs were found in 20% of women who did not report a prior fracture.

VFA is an established method but still not routinely used

Quite recently in Sweden, the National Board of Health and Welfare published new recommendations that the proportion of VFAs in conjunction with central DXA should be 100%.[174] In 2021, DXA devices in Sweden were estimated to be 66 (of which 7 devices are used for research) in a population of 10.4 million, resulting in 5.7 units per million inhabitants.[237] The number of DXA devices varies markedly in different countries and the optimal number of DXA devices for managing osteoporosis was estimated in different scenarios by Kanis and Johnell in 2005.[238] If all women at the age of ≥ 65 years were to be screened (over a 10-year period), the requirement for DXA would be 11.21 units per million. If instead women with strong risk factors for fracture were referred for densitometry (another scenario), the estimated need for DXA devices was 5.36 units per million. In countries outside Europe, the number of DXA / million of the population (2003) varied from 2.3 in Saudi Arabia to 35.6 in the USA and in Europe it ranged between 0.6 in Russia to 20 in France and Portugal. There are also countries worldwide that have fewer than one DXA machine per million

(e.g. Indonesia, Sri Lanka, Pakistan, China, India). Kanis et al. concluded that the availability of DXA globally seems to be sub-optimal, and the most effective use of the devices is the use of CRFs with the selective use of BMD.[238]

The categorisation of fracture risk and choice of treatment

Recently published guidelines suggest that bone specific treatment can be recommended without further assessment by DXA or FRAX in older patients (> 65 years) with a prior low-trauma fracture.[164,239] Would additional knowledge of prevalent VFs change treatment choices in individuals with known prior low-trauma fracture?

Recently, some guidelines have begun to categorise patients into those who are at low, high or very high risk for fracture, due to age-dependent intervention FRAX thresholds, to be able to optimize the treatment.[240] "High risk" patients are usually recommended antiresorptive treatment while "very high risk" patients benefit from anabolic agents, followed by an antiresorptive agent (sequential treatment). As recommended by the International Osteoporosis Foundation (IOF) and the European Society for Clinical and Economic Evaluation of Osteoporosis and Osteoarthritis (ESCEO), the fracture risk should be expressed as an absolute risk, taking age, life expectancy and current fracture risk into account, which preferably can be expressed as the 10-year probability of MOF or hip fracture.[128,164] In Paper IV we evaluated whether VFA-identified VFs in older women affect the 10-year probability of MOF in FRAX independently of self-reported prior fractures and other CRFs used in FRAX and FN BMD. We found that VFA-identified VFs have a considerably impact on the 10-year probability of MOF beyond the risk a prior self-reported fracture contributes with. The 10-year probability of MOF increased from 29.5% (without considering VFA) to 36.7% (having a VFA-identified VF) for a 75-year-old woman with a previous fracture but no other CRFs and BMD T-score -2. But has this new information any importance in the clinical setting? Regarding the algorithm presented in **Figure 25**, a 75-year-old woman with 10-year probability of MOF of approximately 30%, will have a borderline very high to high fracture risk. However, the choice between sequential treatment and antiresorptive medication alone may in clinical

everyday life be difficult. Anabolic drugs are more expensive and require expertise in anti-osteoporotic medication. When VFA is taken into account and the 10-year probability of MOF increases to "very high" without any doubt, more patients at very high risk will probably be considered for sequential treatment, or at least to a greater extent be provided with an optimal treatment plan.

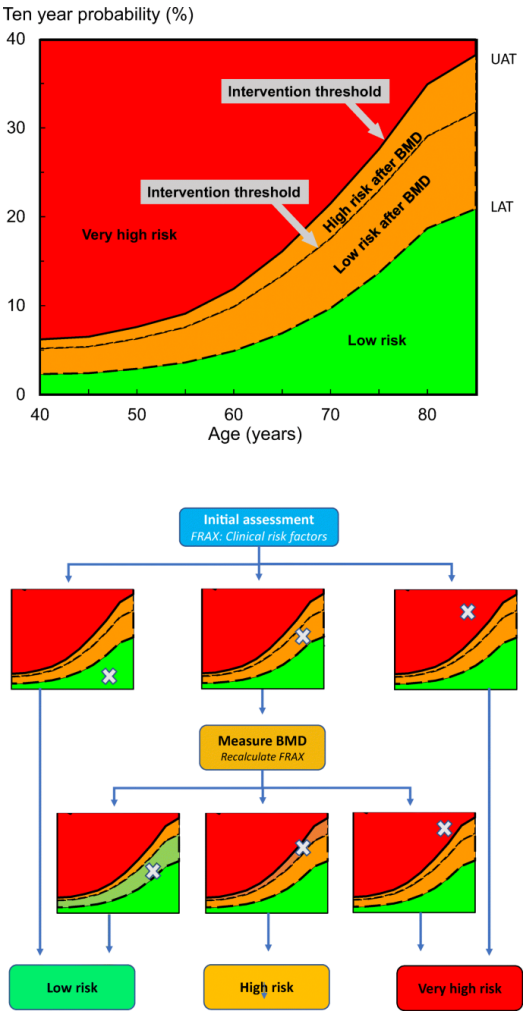


Figure 25. *Infographic outlining of the characterization of fracture risk by FRAX major osteoporotic fracture probability in postmenopausal women. Initial risk assessment uses FRAX with clinical risk factors alone. FRAX probability in the red zone indicates very high risk and that an initial*

course of anabolic treatment followed by antiresorptive therapy may be appropriate. FRAX probability in the green zone suggests low risk, with advice to be given on lifestyle, calcium and vitamin D nutrition and menopausal hormone treatment considered. FRAX probability in the intermediate (orange) zone should be followed by BMD assessment and recalculation of FRAX probability including femoral neck BMD. After recalculation, risk may be in the red zone (very high risk), orange zone (high risk, which suggests initial antiresorptive therapy) or green zone (low risk, either in the original green zone or in the original orange zone but below the intervention threshold). Note that patients with a prior fragility fracture are designated at high risk at least and possibly at very high risk dependent upon the FRAX probability. ***With kind permission of Springer Nature*** [240]

6. Conclusions

VFs are one of the strongest predictors for future fracture. If VFs are identified and effective treatment is initiated, the risk of future fracture can be reduced considerably, by 40-70%, using antiresorptives alone, and with even greater efficiency if sequential treatment is used. More efficient fracture risk prediction and treatment will not only reduce the burden of disability, morbidity, and mortality on an individual level, but also reduce the burden on society, as well as health and welfare costs. By using VFA, in conjunction with DXA, the spine can be evaluated for VFs, and bone-specific treatment can be initiated when appropriate. We investigated whether VFA-identified VFs were associated with bone traits assessed by DXA, HRpQCT and bone microindentation. In concordance with previous studies, which have used conventional x-ray for identifying VFs, TH BMD by DXA was strongly and independently associated with VF in older women, although identified by VFA. We also found that back pain was more common, and that physical health and physical function, assessed by performance-based measurements, were inferior in these women with VFs compared with women without, and that even mild VFs had impact on physical health and function. The clinical utility of VFA was further investigated by examining whether VFA-identified VFs predict future fractures, and more specifically the predictive value of mild VFs. Due to the fact that mild (grade 1) VFs were independently associated with future MOF, we concluded that all VFs, regardless of severity, should be taken into account when assessing fracture risk in older women. However, can a VFA-identified VF improve fracture risk prediction beyond that of a prior fracture put into FRAX? Analyses using FRAX models showed that VFA-identified VFs clearly increased the 10-year probability of MOF independently of CRFs, FN BMD, and prior self-reported fracture. Based on these findings, it may be concluded that VFA is a valuable tool in fracture risk assessment in older women and should be incorporated routinely into clinical practice.

7. Future Perspectives

Even though extensive research has shown evidence of the effectiveness of bone-specific treatment in reducing the risk of future fractures, there is an undertreatment, the so called "treatment gap", of patients who would benefit from osteoporosis medication.[25,241] There are probably several reasons for this, e.g. the fear of adverse events (e.g. osteonecrosis of the jaw, atypical femoral fractures, gastro-intestinal events, atrial fibrillation, cardiovascular events), inadequate knowledge about osteoporosis medication efficacy among clinicians, and the varying extent of reimbursements from health care providers, which may differ both at a national and international level. Studies have indicated also that older and very old patients, who have the highest absolute fracture risk, benefit from bone-specific treatment.[241,242] After a fragility fracture, it is important to start treatment as soon as possible due to the fact that the "imminent risk" of a second fracture is highest in the first 2 years after the first fracture.[137] In a model-based study in postmenopausal women with severe osteoporosis at high risk of fracture, it was shown that treatment with romosozumab followed by alendronate could also be a cost-effective choice in high-risk groups.[243] FLSs play an important role in decreasing the "treatment gap". However, in Sweden, with the highest incidence of osteoporotic fractures in Europe,[1] only 25-50% of hospitals reported the presence of FLSs, and the number DXA units/million inhabitants was 7.4, putting Sweden in twenty-fourth place out of 29 countries.[3] This fact contrasts sharply with the recommendation by the Swedish National Board of Health and Welfare in the most recent guidelines from 2020 stating that the implementation of FLSs (including patient evaluation using DXA) is of the highest priority.[174]

If future studies similar to the one in Paper IV show consistent results regarding the effect of VFA-identified VFs on the 10-year probability of MOF in FRAX, it is possible that VFA results could be incorporated in future FRAX tools. This would further highlight the importance of increased reimbursements for DXA equipment and the education of personnel performing DXA and fracture risk assessments on patients at risk.

Paper IV shows that, having at least one grade 3 VFA-identified VF or ≥ 3 VFA-identified VFs was associated with increased mortality in older

women, independently of CRFs and BMD, which is consistent with previous studies. However, studies on the causes of death in patients with VF are still quite few [244,245], and the SUPERB cohort could perhaps offer the opportunity to evaluate causes of death in patients with VFs.

In Paper I, we found that women with prevalent VFA-identified VFs had impaired trabecular bone microstructure and cortical geometry, assessed by HRpQCT, compared with women without VF, but not independently of TH BMD. There are a few studies examining the predictive value of bone microstructure on incident fractures,[246] although these studies are small and in younger postmenopausal women[247,248], or in older men.[249] Using data from the SUPERB cohort, it would be possible to evaluate the predictive value of HRpQCT on incident fracture in older postmenopausal women in a larger study with longer follow-up time.

When lateral spine images were examined by VFA, the presence of scoliosis also had to be taken into account, since a rotated vertebra may look like a concave VF. The total-body image by DXA was assessed and scoliosis was present when vertebrae deviated clearly laterally from the midline of the spine. With this rather subjective method, 817 individuals from the SUPERB cohort were classified as having scoliosis, which corresponds to a prevalence of 27%. Previous studies are not conclusive as to whether or not VFs predispose scoliosis or scoliosis predisposes weakened vertebrae due to altered mechanical load, which in turn increases the risk for VF.[250] Adult scoliosis is diagnosed in a skeletally mature individual with a Cobb angle of more than 10° in the frontal plane.[251] The prevalence of scoliosis in the population increases with age.[252] To date, scoliosis is not considered a risk factor of VF, and as far as we know, there are no previous studies examining the associations between prevalent scoliosis and incident fractures. It would therefore be warranted to evaluate whether scoliosis and severity of scoliosis in older women are associated with incident vertebral and nonvertebral fractures. However, although we have data on incident fractures, the prevalence of scoliosis in the SUPERB cohort has to be re-evaluated, using the validated method described by Taylor et al.[253,254]

Related publications not included in the thesis

1. Rudang R, Zoulakis M, Sundh D, Brisby H, Diez-Perez A, **Johansson L**, Mellstrom D, Darelid A, Lorentzon M (2016) Bone material strength is associated with areal BMD but not with prevalent fractures in older women. Osteoporos Int 27:1585-1592.

2. Nilsson AG, Sundh D, **Johansson L**, Nilsson M, Mellstrom D, Rudang R, Zoulakis M, Wallander M, Darelid A, Lorentzon M (2017) Type 2 Diabetes Mellitus Is Associated With Better Bone Microarchitecture But Lower Bone Material Strength and Poorer Physical Function in Elderly Women: A Population-Based Study. J Bone Miner Res 32:1062-1071.

3. Sundh D, Nilsson AG, Nilsson M, **Johansson L**, Mellstrom D, Lorentzon M (2017) Increased cortical porosity in women with hip fracture. J Intern Med 281:496-506.

4. Larsson B, Mellstrom D, **Johansson L**, Nilsson AG, Lorentzon M, Sundh D (2018) Normal Bone Microstructure and Density But Worse Physical Function in Older Women Treated with Selective Serotonin Reuptake Inhibitors, a Cross-Sectional Population-Based Study. Calcif Tissue Int 103:278-288.

5. **Johansson L***, Svensson HK*, Karlsson J, Olsson LE, Mellstrom D, Lorentzon M, Sundh D (2019) Decreased physical health-related quality of life-a persisting state for older women with clinical vertebral fracture. Osteoporos Int 30:1961-1971.

6. Larsson BAM, **Johansson L**, Johansson H, Axelsson KF, Harvey N, Vandenput L, Magnusson P, McCloskey E, Liu E, Kanis JA, Sundh D, Lorentzon M (2021) The timed up and go test predicts

fracture risk in older women independently of clinical risk factors and bone mineral density. Osteoporos Int 32:75-84.

7. Larsson BAM, **Johansson L**, Mellstrom D, Johansson H, Axelsson KF, Harvey N, Vandenput L, McCloskey E, Liu E, Sundh D, Kanis JA, Lorentzon M (2022) One leg standing time predicts fracture risk in older women independent of clinical risk factors and BMD. Osteoporos Int 33:185-194.

8. Gullberg J, Sundh D, **Johansson L**, Isberg PE, Lorentzon M, Lindh C (2022) The outcome of an automated assessment of trabecular pattern in intraoral radiographs as a fracture risk predictor. Dentomaxillofac Radiol. Mar 29:20210483. Online ahead of print

* Contributed equally

Acknowledgement

Jag vill rikta ett stort tack till alla de som bidragit till att denna avhandling blivit till.

Ett speciellt tack till min huvudhandledare **Mattias Lorentzon**, som med sitt expertkunnande inom osteoporos och närliggande ämnesområden, sin gedigna erfarenhet av forskning, och med en outtröttlig energi och handlingskraft guidat mig genom denna resa.
Tack **Helena Brisby**, min bi-handledare, för din ryggexpertis i begynnelsen av mitt VFA-analyserande, dina goda råd mot slutet, och din välvilja till att råda när det behövs.
Tack för ekonomisk support från **Vetenskapsrådet**, **ALF/LUA från Sahlgrenska Universitetssjukhuset**, **Inga-Britt och Arne Lundberg forskningsstiftelse**, **Svenska Läkaresällskapet**, **Göteborgs läkaresällskap**, **Kung Gustaf V's och Drottning Victoria's Frimurare stiftelse, Agneta Prytz-Folkes och Gösta Folkes Stiftelse**.
Daniel Sundh, du förtjänar verkligen ett stort innerligt tack. Du har varit till stor hjälp med din kunskap och erfarenhet av HRpQCT, din hjälp med dataprogram och mycket annat. Tack för intressanta forskningsdiskussioner som emellanåt behövs för att lyfta blicken något. Din tålmodighet är beundransvärd.
Anna Nilsson, Du lämnade oss alldeles för tidigt och lämnade ett stort hålrum efter dig. Den värme och medmänsklighet du spred omkring dig var enorm. Ett varmt och innerligt tack för din hjälp och det jag hann lära mig av dig.
Helena Johansson, mycket hade fortfarande varit höljt i dunkel utan din hjälp. Verkligen stort tack för ditt pedagogiska sätt att förklara statistik på, och din tålmodighet när samma frågor upprepas med korta tidsintervall, bra att du kan hänvisa till tidigare mailkorrespondenser!
Tack till min första rumskamrat, **Martin Nilsson**, som på ett föredömligt sätt introducerade mig i validerandets konst. Heder åt noggrannhet, det finns många fallgropar.
I would like to express my sincere gratitude to all my **co-authors** for giving me excellent comments, thoughts and suggestions, thank you!

Ett speciellt tack till **Komagal Rukmangatharajan**, som på ett förtjänstfullt sätt gjorde en tredjedel av alla VFA-analyserna.
Det som förgyllt den här forskningstiden har varit samvaron med alla er på Enheten för osteoporosforskning. Nu kom visserligen en pandemi i vägen så det finns mycket fikasnack och konferenser att ta igen. Utan era fantastiska insatser hade det inte funnits material för mig att skriva avhandling på. Tack **Dan Mellström** för dina anekdoter och gedigna forskningserfarenhet, **Ulrika Hjertonsson** för DXA-undersökningar och ditt ihärdiga CT-bildsanalyserande och allt annat du gör ihärdigt☺, **Linda Kjörling** för DXA-undersökningar och för att du inte fullständigt klappade ihop vid genomgång av alla tusentals röntgensvar, **Maria Falkdal** för genomgång av röntgensvar, allt ditt fixande och att vi kom iväg på roliga konferenser, **Berit Larsson** för alla pratstunder och din spännande mångsidighet, **Kristian Axelsson** för din förmåga att hantera stora datamängder och inte räds IT-problem, allt kan lösas, **Michail Zoulakis** och **Konstantina Kousoula** för trevlig samvaro, **Cecilie Hongslo Vala** för pratstunder om annat än forskning, **Micaela Mattson Westerlund** för din hjälp vid halvtidskontrollen och för trevliga samtal, **Emma Brättemark** och **Lena Silberberg** för erat engagemang i att samordna och insamla forskningsmaterial för kommande spännande studier och för trevlig samvaro.
Tack till **Robin**, **Linn**, **Emelie** och **Amanda** m fl som bidragit till att det överhuvudtaget finns en SUPERB kohort och tack till alla **studiedeltagare**. **Robert Rudäng** och **Anna Darelid**, ni avslutade era avhandlingar när jag började och jag har haft god hjälp av era böcker, tack!
Tack **Jon Karlsson**, för att du initierade kontakten med Mattias Lorentzon.
Mathias Arkeklint, ett stort tack för din ovärderliga och snabba hjälp i samband med datatekniska problem.
Tommy Hansson, dig har jag att tacka för att jag överhuvudtaget började doktorandutbildningen, tack!
Tack **Allison Kaigle Holm**, för att du i ett tidigare projekt introducerade mig till forskningsvärlden och att du med ditt engagemang och noggrannhet lät mig förstå att man inte skall lämna något åt slumpen.
Lena Hörnestam, tack för ditt rumskamratliga stöd i stort och smått och bra samarbete. Tack **Tony Jarl**, för dina glada tillrop under resans gång. Det har betytt mer än vad du nog kan tro.

Tidigare och nuvarande verksamhetschef på Ortopeden, **Magnus Karlsson**, **Henrik Malchau** och **Anna Nilsdotter**, sektionschef **Tuuli Saari** och **schemaläggare**, erat stöd har bidragit till att jag kunnat skriva denna avhandling, tack!

Tack till alla mina **kollegor och medarbetare** på Ortopedkliniken och protesteamet, som bidrar till en trevlig arbetsmiljö. Jag hoppas på mer samvaro framöver. Och till alla **BAD-tjejerna**, tack för härliga stunder i vått, torrt, kallt och varmt. Och till mina tre rumskamrater **Karin**, **Karin** och **Karin** (japp, stämmer), tack för stunder av support och trevliga samtal.

Tack till **Margaret Myers** för språkgranskning, **Anette Nilsson** för hjälp med omslaget m.m. och **Pontus Andersson** för illustrationer.

Daniel Björkdahl och Lundby Motettkör, ni är mitt andningshål; andning och sång ger ny energi, tack!

Rapphönorna, ni är mina sanna förebilder, tack! Tack till de av er som ställde upp som kontrollpersoner i ett tidigare projekt.

Till mina föräldrar, **Inger och Manne Stenberg**, mina systrar **Ingrid Heath och Karin Wannerskog**, ett innerligt djupt tack för allt ni gjort och gör, och för att ni finns där.

Petter, Linnea och Emil, mina allra, allra käraste. Ni har uppvisat ett sådant oerhört tålamod och förståelse under denna process. Jag är så evigt tacksam att ni finns i min närhet, mitt djupaste och innerligaste tack!

References

1. Borgstrom F, Karlsson L, Ortsater G, Norton N, Halbout P, Cooper C, et al. Fragility fractures in Europe: burden, management and opportunities. Arch Osteoporos. Apr 19 2020;15(1):59. Epub 2020/04/20.

2. Kanis JA, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, et al. SCOPE 2021: a new scorecard for osteoporosis in Europe. Arch Osteoporos. Jun 2 2021;16(1):82. Epub 2021/06/04.

3. Willers C, Norton N, Harvey NC, Jacobson T, Johansson H, Lorentzon M, et al. Osteoporosis in Europe: a compendium of country-specific reports. Arch Osteoporos. Jan 26 2022;17(1):23. Epub 2022/01/27.

4. Sanders KM, Pasco JA, Ugoni AM, Nicholson GC, Seeman E, Martin TJ, et al. The exclusion of high trauma fractures may underestimate the prevalence of bone fragility fractures in the community: the Geelong Osteoporosis Study. J Bone Miner Res. Aug 1998;13(8):1337-42. Epub 1998/08/26.

5. Leslie WD, Schousboe JT, Morin SN, Martineau P, Lix LM, Johansson H, et al. Fracture risk following high-trauma versus low-trauma fracture: a registry-based cohort study. Osteoporos Int. Jun 2020;31(6):1059-67. Epub 2020/03/17.

6. Kanis JA, Borgstrom F, De Laet C, Johansson H, Johnell O, Jonsson B, et al. Assessment of fracture risk. Osteoporos Int. Jun 2005;16(6):581-9. Epub 2004/12/24.

7. Kanis JA, Johnell O, Oden A, Sembo I, Redlund-Johnell I, Dawson A, et al. Long-term risk of osteoporotic fracture in Malmo. Osteoporos Int. 2000;11(8):669-74. Epub 2000/11/30.

8. Suzuki T, Yoshida H. Low bone mineral density at femoral neck is a predictor of increased mortality in elderly Japanese women. Osteoporos Int. Jan 2010;21(1):71-9. Epub 2009/06/06.

9. Cooper C, Atkinson EJ, Jacobsen SJ, O'Fallon WM, Melton LJ, 3rd. Population-based study of survival after osteoporotic fractures. Am J Epidemiol. May 1 1993;137(9):1001-5. Epub 1993/05/01.

10. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet. Mar 13 1999;353(9156):878-82. Epub 1999/03/27.

11. Leboime A, Confavreux CB, Mehsen N, Paccou J, David C, Roux C. Osteoporosis and mortality. Joint Bone Spine. Dec 2010;77 Suppl 2:S107-12. Epub 2011/01/08.

12. Kado DM, Browner WS, Palermo L, Nevitt MC, Genant HK, Cummings SR. Vertebral fractures and mortality in older women: a prospective study. Study of Osteoporotic Fractures Research Group. Arch Intern Med. Jun 14 1999;159(11):1215-20. Epub 1999/06/17.

13. Cunningham TD, Martin BC, DeShields SC, Romero CC. The impact of osteoporotic fractures compared with other health conditions in older adults living in Virginia, United States. Osteoporos Int. May 10 2016.

14. Cooper C, Atkinson EJ, O'Fallon WM, Melton LJ, 3rd. Incidence of clinically diagnosed vertebral fractures: a population-based study in Rochester, Minnesota, 1985-1989. J Bone Miner Res. Feb 1992;7(2):221-7.

15. Melton LJ, 3rd, Kan SH, Frye MA, Wahner HW, O'Fallon WM, Riggs BL. Epidemiology of vertebral fractures in women. Am J Epidemiol. May 1989;129(5):1000-11.

16. Melton LJ, 3rd. Epidemiology of spinal osteoporosis. Spine (Phila Pa 1976). Dec 15 1997;22(24 Suppl):2S-11S.

17. O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ. The prevalence of vertebral deformity in european men and women: the European Vertebral Osteoporosis Study. J Bone Miner Res. Jul 1996;11(7):1010-8.

18. Jones G, White C, Nguyen T, Sambrook PN, Kelly PJ, Eisman JA. Prevalent vertebral deformities: relationship to bone mineral density and spinal osteophytosis in elderly men and women. Osteoporos Int. 1996;6(3):233-9. Epub 1996/01/01.

19. Ettinger B, Black DM, Nevitt MC, Rundle AC, Cauley JA, Cummings SR, et al. Contribution of vertebral deformities to chronic back pain and disability. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res. Apr 1992;7(4):449-56. Epub 1992/04/01.

20. Klotzbuecher CM, Ross PD, Landsman PB, Abbott TA, 3rd, Berger M. Patients with prior fractures have an increased risk of future fractures: a summary of the literature and statistical synthesis. J Bone Miner Res. Apr 2000;15(4):721-39.

21. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA. Feb 4 2009;301(5):513-21. Epub 2009/02/05.

22. Pongchaiyakul C, Nguyen ND, Jones G, Center JR, Eisman JA, Nguyen TV. Asymptomatic vertebral deformity as a major risk factor for subsequent fractures and mortality: a long-term prospective study. J Bone Miner Res. Aug 2005;20(8):1349-55. Epub 2005/07/12.

23. Ross PD. Clinical consequences of vertebral fractures. Am J Med. Aug 18 1997;103(2A):30S-42S; discussion S-3S.

24. Al-Sari UA, Tobias J, Clark E. Health-related quality of life in older people with osteoporotic vertebral fractures: a systematic review and meta-analysis. Osteoporos Int. Oct 2016;27(10):2891-900.

25. Lorentzon M, Nilsson AG, Johansson H, Kanis JA, Mellstrom D, Sundh D. Extensive undertreatment of osteoporosis in older Swedish women. Osteoporos Int. Jun 2019;30(6):1297-305. Epub 2019/02/26.

26. Buck DW, 2nd, Dumanian GA. Bone biology and physiology: Part I. The fundamentals. Plast Reconstr Surg. Jun 2012;129(6):1314-20. Epub 2012/05/29.

27. Florencio-Silva R, Sasso GR, Sasso-Cerri E, Simoes MJ, Cerri PS. Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. Biomed Res Int. 2015;2015:421746. Epub 2015/08/08.

28. Clarke B. Normal bone anatomy and physiology. Clin J Am Soc Nephrol. Nov 2008;3 Suppl 3:S131-9. Epub 2008/11/15.

29. Langdahl B, Ferrari S, Dempster DW. Bone modeling and remodeling: potential as therapeutic targets for the treatment of osteoporosis. Ther Adv Musculoskelet Dis. Dec 2016;8(6):225-35. Epub 2017/03/04.

30. Baron R, Hesse E. Update on bone anabolics in osteoporosis treatment: rationale, current status, and perspectives. J Clin Endocrinol Metab. Feb 2012;97(2):311-25. Epub 2012/01/13.

31. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev. Apr 2000;21(2):115-37. Epub 2000/04/27.

32. Bonewald LF. The amazing osteocyte. J Bone Miner Res. Feb 2011;26(2):229-38. Epub 2011/01/22.

33. Nakashima T, Hayashi M, Fukunaga T, Kurata K, Oh-Hora M, Feng JQ, et al. Evidence for osteocyte regulation of bone homeostasis through RANKL expression. Nat Med. Sep 11 2011;17(10):1231-4. Epub 2011/09/13.

34. Cheng CH, Chen LR, Chen KH. Osteoporosis Due to Hormone Imbalance: An Overview of the Effects of Estrogen Deficiency and Glucocorticoid Overuse on Bone Turnover. Int J Mol Sci. Jan 25 2022;23(3). Epub 2022/02/16.

35. Lindsey RC, Mohan S. Skeletal effects of growth hormone and insulin-like growth factor-I therapy. Mol Cell Endocrinol. Sep 5 2016;432:44-55. Epub 2015/09/27.

36. Hsiao CY, Chen TH, Chu TH, Ting YN, Tsai PJ, Shyu JF. Calcitonin Induces Bone Formation by Increasing Expression of Wnt10b in Osteoclasts in Ovariectomy-Induced Osteoporotic Rats. Front Endocrinol (Lausanne). 2020;11:613. Epub 2020/10/06.

37. Eisman JA, Bouillon R. Vitamin D: direct effects of vitamin D metabolites on bone: lessons from genetically modified mice. Bonekey Rep. 2014;3:499. Epub 2014/03/08.

38. Cianferotti L, Cricelli C, Kanis JA, Nuti R, Reginster JY, Ringe JD, et al. The clinical use of vitamin D metabolites and their potential developments: a position statement from the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) and the International Osteoporosis Foundation (IOF). Endocrine. Sep 2015;50(1):12-26. Epub 2015/05/02.

39. Kuzma M, Jackuliak P, Killinger Z, Payer J. Parathyroid Hormone-Related Changes of Bone Structure. Physiol Res. Nov 30 2021;70(Suppl 1):S3-S11. Epub 2021/12/18.

40. Schapira D, Schapira C. Osteoporosis: the evolution of a scientific term. Osteoporos Int. Jul 1992;2(4):164-7. Epub 1992/07/01.

41. Jha S, Chapman M, Roszko K. When Low Bone Mineral Density and Fractures Is Not Osteoporosis. Curr Osteoporos Rep. Oct 2019;17(5):324-32. Epub 2019/08/31.

42. Lorentzon M, Cummings SR. Osteoporosis: the evolution of a diagnosis. J Intern Med. Jun 2015;277(6):650-61. Epub 2015/04/03.

43. Manring MM, Calhoun JH. Biographical sketch: Fuller Albright, MD 1900-1969. Clin Orthop Relat Res. Aug 2011;469(8):2092-5. Epub 2011/03/09.

44. Forbes AP. Fuller Albright. His concept of postmenopausal osteoporosis and what came of it. Clin Orthop Relat Res. Aug 1991(269):128-41. Epub 1991/08/01.

45. Wasnich RD, Ross PD, Heilbrun LK, Vogel JM. Selection of the optimal skeletal site for fracture risk prediction. Clin Orthop Relat Res. Mar 1987(216):262-9. Epub 1987/03/01.

46. Hui SL, Slemenda CW, Johnston CC, Jr. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest. Jun 1988;81(6):1804-9. Epub 1988/06/01.

47. Kleerekoper M, Villanueva AR, Stanciu J, Rao DS, Parfitt AM. The role of three-dimensional trabecular microstructure in the pathogenesis of vertebral compression fractures. Calcif Tissue Int. Dec 1985;37(6):594-7.

48. Consensus development conference: prophylaxis and treatment of osteoporosis. Am J Med. Jan 1991;90(1):107-10. Epub 1991/01/01.

49. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser. 1994;843:1-129. Epub 1994/01/01.

50. Nih Consensus Development Panel on Osteoporosis Prevention D, Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA. Feb 14 2001;285(6):785-95. Epub 2001/02/15.

51. Cooper C, Melton LJ, 3rd. Epidemiology of osteoporosis. Trends Endocrinol Metab. Aug 1992;3(6):224-9.

52. Njeh CF, Fuerst T, Hans D, Blake GM, Genant HK. Radiation exposure in bone mineral density assessment. Appl Radiat Isot. Jan 1999;50(1):215-36. Epub 1999/02/24.

53. Franck H, Munz M, Scherrer M, v Lilienfeld-Toal H. Lateral spine dual-energy X-ray absorptiometry bone mineral measurement with fan-beam design: effect of osteophytic calcifications on lateral and anteroposterior spine BMD. Rheumatol Int. 1995;15(4):151-4. Epub 1995/01/01.

54. Pothuaud L, Carceller P, Hans D. Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture. Bone. Apr 2008;42(4):775-87.

55. Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, et al. Trabecular bone score: a noninvasive analytical method based upon the DXA image. J Bone Miner Res. Mar 2014;29(3):518-30. Epub 2014/01/21.

56. Hans D, Goertzen AL, Krieg MA, Leslie WD. Bone microarchitecture assessed by TBS predicts osteoporotic fractures independent of bone density: the Manitoba study. J Bone Miner Res. Nov 2011;26(11):2762-9.

57. McCloskey EV, Oden A, Harvey NC, Leslie WD, Hans D, Johansson H, et al. A Meta-Analysis of Trabecular Bone Score in Fracture Risk Prediction and Its Relationship to FRAX. J Bone Miner Res. May 2016;31(5):940-8. Epub 2015/10/27.

58. Krohn K, Schwartz EN, Chung YS, Lewiecki EM. Dual-energy X-ray Absorptiometry Monitoring with Trabecular Bone Score: 2019 ISCD Official Position. J Clin Densitom. Oct - Dec 2019;22(4):501-5. Epub 2019/08/07.

59. Jergas M, Uffmann M, Escher H, Gluer CC, Young KC, Grampp S, et al. Interobserver variation in the detection of osteopenia by radiography and comparison with dual X-ray absorptiometry of the lumbar spine. Skeletal Radiol. Apr 1994;23(3):195-9. Epub 1994/04/01.

60. Genant HK, Li J, Wu CY, Shepherd JA. Vertebral fractures in osteoporosis: a new method for clinical assessment. J Clin Densitom. Fall 2000;3(3):281-90.

61. Parfitt AM, Mathews CH, Villanueva AR, Kleerekoper M, Frame B, Rao DS. Relationships between surface, volume, and thickness of iliac trabecular bone in aging and in osteoporosis. Implications for the microanatomic and cellular mechanisms of bone loss. J Clin Invest. Oct 1983;72(4):1396-409.

62. Parfitt AM. Trabecular bone architecture in the pathogenesis and prevention of fracture. Am J Med. Jan 26 1987;82(1B):68-72.

63. Compston JE, Mellish RW, Garrahan NJ. Age-related changes in iliac crest trabecular microanatomic bone structure in man. Bone. 1987;8(5):289-92. Epub 1987/01/01.

64. Mosekilde L, Mosekilde L, Danielsen CC. Biomechanical competence of vertebral trabecular bone in relation to ash density and age in normal individuals. Bone. 1987;8(2):79-85.

65. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, March 7-29, 2000: highlights of the conference. South Med J. Jun 2001;94(6):569-73. Epub 2001/07/07.

66. Ruegsegger P, Elsasser U, Anliker M, Gnehm H, Kind H, Prader A. Quantification of bone mineralization using computed tomography. Radiology. Oct 1976;121(1):93-7. Epub 1976/10/01.

67. Adams JE. Quantitative computed tomography. Eur J Radiol. Sep 2009;71(3):415-24. Epub 2009/08/18.

68. Engelke K, Adams JE, Armbrecht G, Augat P, Bogado CE, Bouxsein ML, et al. Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2007 ISCD Official Positions. J Clin Densitom. Jan-Mar 2008;11(1):123-62. Epub 2008/04/30.

69. Muller A, Ruegsegger E, Ruegsegger P. Peripheral QCT: a low-risk procedure to identify women predisposed to osteoporosis. Phys Med Biol. Jun 1989;34(6):741-9. Epub 1989/06/01.

70. Muller R, Hildebrand T, Ruegsegger P. Non-invasive bone biopsy: a new method to analyse and display the three-dimensional structure of trabecular bone. Phys Med Biol. Jan 1994;39(1):145-64. Epub 1994/01/01.

71. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In vivo assessment of trabecular bone microarchitecture by high-resolution peripheral quantitative computed tomography. J Clin Endocrinol Metab. Dec 2005;90(12):6508-15.

72. Laib A, Hauselmann HJ, Ruegsegger P. In vivo high resolution 3D-QCT of the human forearm. Technol Health Care. Dec 1998;6(5-6):329-37.

73. MacNeil JA, Boyd SK. Accuracy of high-resolution peripheral quantitative computed tomography for measurement of bone quality. Med Eng Phys. Dec 2007;29(10):1096-105.

74. Hansma P, Turner P, Drake B, Yurtsev E, Proctor A, Mathews P, et al. The bone diagnostic instrument II: indentation distance increase. Rev Sci Instrum. Jun 2008;79(6):064303. Epub 2008/07/08.

75. Zysset PK. Indentation of bone tissue: a short review. Osteoporos Int. Jun 2009;20(6):1049-55. Epub 2009/04/03.

76. Diez-Perez A, Guerri R, Nogues X, Caceres E, Pena MJ, Mellibovsky L, et al. Microindentation for in vivo measurement of bone tissue mechanical properties in humans. J Bone Miner Res. Aug 2010;25(8):1877-85.

77. Bridges D, Randall C, Hansma PK. A new device for performing reference point indentation without a reference probe. Rev Sci Instrum. Apr 2012;83(4):044301.

78. Rudang R, Zoulakis M, Sundh D, Brisby H, Diez-Perez A, Johansson L, et al. Bone material strength is associated with areal BMD but not with prevalent fractures in older women. Osteoporos Int. Apr 2016;27(4):1585-92.

79. Malgo F, Hamdy NA, Papapoulos SE, Appelman-Dijkstra NM. Bone material strength as measured by microindentation in vivo is decreased in patients with fragility fractures independently of bone mineral density. J Clin Endocrinol Metab. May 2015;100(5):2039-45.

80. Allen MR, McNerny EM, Organ JM, Wallace JM. True Gold or Pyrite: A Review of Reference Point Indentation for Assessing Bone Mechanical Properties In Vivo. J Bone Miner Res. Sep 2015;30(9):1539-50.

81. Arnold M, Zhao S, Ma S, Giuliani F, Hansen U, Cobb JP, et al. Microindentation - a tool for measuring cortical bone stiffness? A systematic review. Bone Joint Res. Sep 2017;6(9):542-9. Epub 2017/09/20.

82. Morita R, Yamamoto I, Yuu I, Hamanaka Y, Ohta T, Takada M, et al. Quantitative ultrasound for the assessment of bone status. Osteoporos Int. 1997;7 Suppl 3:S128-34. Epub 1997/01/01.

83. Krieg MA, Barkmann R, Gonnelli S, Stewart A, Bauer DC, Del Rio Barquero L, et al. Quantitative ultrasound in the management of osteoporosis: the 2007 ISCD Official Positions. J Clin Densitom. Jan-Mar 2008;11(1):163-87. Epub 2008/04/30.

84. Gluer CC, Eastell R, Reid DM, Felsenberg D, Roux C, Barkmann R, et al. Association of five quantitative ultrasound devices and bone densitometry with osteoporotic vertebral fractures in a population-based sample: the OPUS Study. J Bone Miner Res. May 2004;19(5):782-93. Epub 2004/04/08.

85. Nguyen HG, Lieu KB, Ho-Le TP, Ho-Pham LT, Nguyen TV. Discordance between quantitative ultrasound and dual-energy X-ray absorptiometry in bone mineral density: The Vietnam Osteoporosis Study. Osteoporos Sarcopenia. Mar 2021;7(1):6-10. Epub 2021/04/20.

86. Kanis JA, Melton LJ, 3rd, Christiansen C, Johnston CC, Khaltaev N. The diagnosis of osteoporosis. J Bone Miner Res. Aug 1994;9(8):1137-41. Epub 1994/08/01.

87. Bonjour JP, Theintz G, Law F, Slosman D, Rizzoli R. Peak bone mass. Osteoporos Int. 1994;4 Suppl 1:7-13. Epub 1994/01/01.

88. Lorentzon M, Mellstrom D, Ohlsson C. Age of attainment of peak bone mass is site specific in Swedish men--The GOOD study. J Bone Miner Res. Jul 2005;20(7):1223-7. Epub 2005/06/09.

89. Lin YC, Lyle RM, Weaver CM, McCabe LD, McCabe GP, Johnston CC, et al. Peak spine and femoral neck bone mass in young women. Bone. May 2003;32(5):546-53. Epub 2003/05/20.

90. Ohlsson C, Darelid A, Nilsson M, Melin J, Mellstrom D, Lorentzon M. Cortical consolidation due to increased mineralization and endosteal contraction in young adult men: a five-year longitudinal study. J Clin Endocrinol Metab. Jul 2011;96(7):2262-9. Epub 2011/05/14.

91. Nguyen TV, Maynard LM, Towne B, Roche AF, Wisemandle W, Li J, et al. Sex differences in bone mass acquisition during growth: the Fels Longitudinal Study. J Clin Densitom. Summer 2001;4(2):147-57. Epub 2001/07/31.

92. Rizzoli R, Bonjour JP, Ferrari SL. Osteoporosis, genetics and hormones. J Mol Endocrinol. Apr 2001;26(2):79-94. Epub 2001/03/10.

93. Nilsson M, Ohlsson C, Oden A, Mellstrom D, Lorentzon M. Increased physical activity is associated with enhanced development of peak bone mass in men: a five-year longitudinal study. J Bone Miner Res. May 2012;27(5):1206-14. Epub 2012/01/17.

94. Gallagher JC, Goldgar D, Moy A. Total bone calcium in normal women: effect of age and menopause status. J Bone Miner Res. Dec 1987;2(6):491-6. Epub 1987/12/01.

95. Aaron JE, Johnson DR, Paxton S, Kanis JA. Secondary osteoporosis and the microanatomy of trabecular bone. Clin Rheumatol. Jun 1989;8 Suppl 2:84-8. Epub 1989/06/01.

96. Schousboe JT. Epidemiology of Vertebral Fractures. J Clin Densitom. Jan-Mar 2016;19(1):8-22. Epub 2015/09/10.

97. Hasserius R, Karlsson MK, Nilsson BE, Redlund-Johnell I, Johnell O, European Vertebral Osteoporosis S. Prevalent vertebral deformities predict increased mortality and increased fracture rate in both men and women: a 10-year population-based study of 598 individuals from the Swedish cohort in the European Vertebral Osteoporosis Study. Osteoporos Int. Jan 2003;14(1):61-8.

98. Cauley JA, Thompson DE, Ensrud KC, Scott JC, Black D. Risk of mortality following clinical fractures. Osteoporos Int. 2000;11(7):556-61. Epub 2000/11/09.

99. Waterloo S, Sogaard AJ, Ahmed LA, Damsgard E, Morseth B, Emaus N. Vertebral fractures and self-perceived health in elderly women and men in a population-based cross-sectional study: the Tromso Study 2007-08. BMC Geriatr. 2013;13:102.

100. Johansson L, Svensson HK, Karlsson J, Olsson LE, Mellstrom D, Lorentzon M, et al. Decreased physical health-related quality of life-a persisting state for older women with clinical vertebral fracture. Osteoporos Int. Oct 2019;30(10):1961-71. Epub 2019/06/23.

101. Judith E Adams LL, Christian Roux and Harry K. Genant International Osteoporosis Foundation. Vertebral Fracture Initiative Part II Radiological Assessment of Vertebral Fracture 2011.

102. Eastell R, Cedel SL, Wahner HW, Riggs BL, Melton LJ, 3rd. Classification of vertebral fractures. J Bone Miner Res. Mar 1991;6(3):207-15.

103. McCloskey EV, Spector TD, Eyres KS, Fern ED, O'Rourke N, Vasikaran S, et al. The assessment of vertebral deformity: a method for use in population studies and clinical trials. Osteoporos Int. May 1993;3(3):138-47. Epub 1993/05/01.

104. Black DM, Cummings SR, Stone K, Hudes E, Palermo L, Steiger P. A new approach to defining normal vertebral dimensions. J Bone Miner Res. Aug 1991;6(8):883-92.

105. Chou SH, Vokes T. Vertebral Morphometry. J Clin Densitom. Jan-Mar 2016;19(1):48-53. Epub 2015/09/10.

106. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. Sep 1993;8(9):1137-48.

107. Jiang G, Eastell R, Barrington NA, Ferrar L. Comparison of methods for the visual identification of prevalent vertebral fracture in osteoporosis. Osteoporos Int. Nov 2004;15(11):887-96.

108. Melton LJ, 3rd, Wenger DE, Atkinson EJ, Achenbach SJ, Berquist TH, Riggs BL, et al. Influence of baseline deformity definition on subsequent vertebral fracture risk in postmenopausal women. Osteoporos Int. 2006;17(7):978-85. Epub 2006/06/08.

109. Black DM, Palermo L, Nevitt MC, Genant HK, Epstein R, San Valentin R, et al. Comparison of methods for defining prevalent vertebral deformities: the Study of Osteoporotic Fractures. J Bone Miner Res. Jun 1995;10(6):890-902. Epub 1995/06/01.

110. Stone KL, Seeley DG, Lui LY, Cauley JA, Ensrud K, Browner WS, et al. BMD at multiple sites and risk of fracture of multiple types: long-term results from the Study of Osteoporotic Fractures. J Bone Miner Res. Nov 2003;18(11):1947-54. Epub 2003/11/11.

111. Padlina I, Gonzalez-Rodriguez E, Hans D, Metzger M, Stoll D, Aubry-Rozier B, et al. The lumbar spine age-related degenerative disease influences the BMD not the TBS: the Osteolaus cohort. Osteoporos Int. Mar 2017;28(3):909-15.

112. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, et al. Risk of new vertebral fracture in the year following a fracture. JAMA. Jan 17 2001;285(3):320-3.

113. Cheng XG, Nicholson PH, Boonen S, Lowet G, Brys P, Aerssens J, et al. Prediction of vertebral strength in vitro by spinal bone densitometry and calcaneal ultrasound. J Bone Miner Res. Oct 1997;12(10):1721-8. Epub 1997/10/23.

114. Briggs AM, Greig AM, Wark JD. The vertebral fracture cascade in osteoporosis: a review of aetiopathogenesis. Osteoporos Int. May 2007;18(5):575-84. Epub 2007/01/09.

115. Roux C, Fechtenbaum J, Kolta S, Said-Nahal R, Briot K, Benhamou CL. Prospective assessment of thoracic kyphosis in postmenopausal women with osteoporosis. J Bone Miner Res. Feb 2010;25(2):362-8. Epub 2009/07/15.

116. Broy SB. The Vertebral Fracture Cascade: Etiology and Clinical Implications. J Clin Densitom. Jan-Mar 2016;19(1):29-34.

117. Adams MA, Pollintine P, Tobias JH, Wakley GK, Dolan P. Intervertebral disc degeneration can predispose to anterior vertebral fractures in the thoracolumbar spine. J Bone Miner Res. Sep 2006;21(9):1409-16. Epub 2006/08/31.

118. Takegami N, Akeda K, Murata K, Yamada J, Sudo A. Association between non-traumatic vertebral fractures and adjacent discs degeneration: a cross-sectional study and literature review. BMC Musculoskelet Disord. Nov 27 2020;21(1):781. Epub 2020/11/29.

119. Griffith JF. Identifying osteoporotic vertebral fracture. Quant Imaging Med Surg. Aug 2015;5(4):592-602.

120. Diacinti D, Acca M, D'Erasmo E, Tomei E, Mazzuoli GF. Aging changes in vertebral morphometry. Calcif Tissue Int. Dec 1995;57(6):426-9. Epub 1995/12/01.

121. Ferrar L, Jiang G, Armbrecht G, Reid DM, Roux C, Gluer CC, et al. Is short vertebral height always an osteoporotic fracture? The Osteoporosis and Ultrasound Study (OPUS). Bone. Jul 2007;41(1):5-12. Epub 2007/05/15.

122. Abdel-Hamid Osman A, Bassiouni H, Koutri R, Nijs J, Geusens P, Dequeker J. Aging of the thoracic spine: distinction between wedging in osteoarthritis and fracture in osteoporosis--a cross-sectional and longitudinal study. Bone. Jul-Aug 1994;15(4):437-42.

123. Chan KK, Sartoris DJ, Haghighi P, Sledge P, Barrett-Connor E, Trudell DT, et al. Cupid's bow contour of the vertebral body: evaluation of pathogenesis with bone densitometry and imaging-histopathologic correlation. Radiology. Jan 1997;202(1):253-6. Epub 1997/01/01.

124. Cranney A, Jamal SA, Tsang JF, Josse RG, Leslie WD. Low bone mineral density and fracture burden in postmenopausal women. CMAJ. Sep 11 2007;177(6):575-80. Epub 2007/09/12.

125. Eriksen EF. Treatment of osteopenia. Rev Endocr Metab Disord. Sep 2012;13(3):209-23. Epub 2011/06/29.

126. Kanis JA, Johnell O, Oden A, Jonsson B, De Laet C, Dawson A. Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis. Bone. Nov 2000;27(5):585-90. Epub 2000/11/04.

127. Kanis JA, Black D, Cooper C, Dargent P, Dawson-Hughes B, De Laet C, et al. A new approach to the development of assessment guidelines for osteoporosis. Osteoporos Int. Jul 2002;13(7):527-36. Epub 2002/07/12.

128. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int. Apr 2008;19(4):385-97.

129. Kanis JA, Harvey NC, Johansson H, Liu E, Vandenput L, Lorentzon M, et al. A decade of FRAX: how has it changed the management of osteoporosis? Aging Clin Exp Res. Feb 2020;32(2):187-96. Epub 2020/02/12.

130. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int. Dec 2001;12(12):989-95. Epub 2002/02/16.

131. De Laet C, Oden A, Johansson H, Johnell O, Jonsson B, Kanis JA. The impact of the use of multiple risk indicators for fracture on case-finding strategies: a mathematical approach. Osteoporos Int. Mar 2005;16(3):313-8. Epub 2004/07/09.

132. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, et al. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. N Engl J Med. Mar 23 1995;332(12):767-73. Epub 1995/03/23.

133. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. BMJ. May 18 1996;312(7041):1254-9. Epub 1996/05/18.

134. Johnell O, Kanis JA, Oden A, Johansson H, De Laet C, Delmas P, et al. Predictive value of BMD for hip and other fractures. J Bone Miner Res. Jul 2005;20(7):1185-94. Epub 2005/06/09.

135. De Laet C, Kanis JA, Oden A, Johanson H, Johnell O, Delmas P, et al. Body mass index as a predictor of fracture risk: a meta-analysis. Osteoporos Int. Nov 2005;16(11):1330-8. Epub 2005/06/02.

136. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone. Aug 2004;35(2):375-82.

137. Johansson H, Siggeirsdottir K, Harvey NC, Oden A, Gudnason V, McCloskey E, et al. Imminent risk of fracture after fracture. Osteoporos Int. Mar 2017;28(3):775-80. Epub 2016/12/29.

138. Kanis JA, Johansson H, Oden A, Johnell O, De Laet C, Eisman JA, et al. A family history of fracture and fracture risk: a meta-analysis. Bone. Nov 2004;35(5):1029-37. Epub 2004/11/16.

139. Kanis JA, Johnell O, Oden A, Johansson H, De Laet C, Eisman JA, et al. Smoking and fracture risk: a meta-analysis. Osteoporos Int. Feb 2005;16(2):155-62. Epub 2004/06/04.

140. Kanis JA, Johansson H, Johnell O, Oden A, De Laet C, Eisman JA, et al. Alcohol intake as a risk factor for fracture. Osteoporos Int. Jul 2005;16(7):737-42. Epub 2004/09/30.

141. Kanis JA, Johansson H, Oden A, Johnell O, de Laet C, Melton IL, et al. A meta-analysis of prior corticosteroid use and fracture risk. J Bone Miner Res. Jun 2004;19(6):893-9. Epub 2004/05/06.

142. van Staa TP, Leufkens HG, Cooper C. The epidemiology of corticosteroid-induced osteoporosis: a meta-analysis. Osteoporos Int. Oct 2002;13(10):777-87. Epub 2002/10/16.

143. https://www.sheffield.ac.uk/FRAX/.

144. Kanis JA, Oden A, Johnell O, Johansson H, De Laet C, Brown J, et al. The use of clinical risk factors enhances the performance of BMD in the prediction

of hip and osteoporotic fractures in men and women. Osteoporos Int. Aug 2007;18(8):1033-46. Epub 2007/02/27.

145. Kanis JA, Johansson H, Oden A, McCloskey EV. Guidance for the adjustment of FRAX according to the dose of glucocorticoids. Osteoporos Int. Mar 2011;22(3):809-16. Epub 2011/01/14.

146. Kanis JA, Johansson H, Harvey NC, Gudnason V, Sigurdsson G, Siggeirsdottir K, et al. Adjusting conventional FRAX estimates of fracture probability according to the recency of sentinel fractures. Osteoporos Int. Oct 2020;31(10):1817-28. Epub 2020/07/03.

147. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA. Spine-hip discordance and fracture risk assessment: a physician-friendly FRAX enhancement. Osteoporos Int. Mar 2011;22(3):839-47. Epub 2010/10/21.

148. Vokes T, Bachman D, Baim S, Binkley N, Broy S, Ferrar L, et al. Vertebral fracture assessment: the 2005 ISCD Official Positions. J Clin Densitom. Jan-Mar 2006;9(1):37-46. Epub 2006/05/30.

149. Lewiecki EM, Laster AJ. Clinical review: Clinical applications of vertebral fracture assessment by dual-energy x-ray absorptiometry. J Clin Endocrinol Metab. Nov 2006;91(11):4215-22. Epub 2006/08/31.

150. Schousboe JT, Vokes T, Broy SB, Ferrar L, McKiernan F, Roux C, et al. Vertebral Fracture Assessment: the 2007 ISCD Official Positions. J Clin Densitom. Jan-Mar 2008;11(1):92-108.

151. Rea JA, Li J, Blake GM, Steiger P, Genant HK, Fogelman I. Visual assessment of vertebral deformity by X-ray absorptiometry: a highly predictive method to exclude vertebral deformity. Osteoporos Int. 2000;11(8):660-8.

152. Vokes TJ, Dixon LB, Favus MJ. Clinical utility of dual-energy vertebral assessment (DVA). Osteoporos Int. Nov 2003;14(11):871-8.

153. Hospers IC, van der Laan JG, Zeebregts CJ, Nieboer P, Wolffenbuttel BH, Dierckx RA, et al. Vertebral fracture assessment in supine position: comparison by using conventional semiquantitative radiography and visual radiography. Radiology. Jun 2009;251(3):822-8. Epub 2009/04/22.

154. Blake GM, Rea JA, Fogelman I. Vertebral morphometry studies using dual-energy x-ray absorptiometry. Semin Nucl Med. Jul 1997;27(3):276-90.

155. McLellan AR, Gallacher SJ, Fraser M, McQuillian C. The fracture liaison service: success of a program for the evaluation and management of patients

with osteoporotic fracture. Osteoporos Int. Dec 2003;14(12):1028-34. Epub 2003/11/06.

156. Wu CH, Tu ST, Chang YF, Chan DC, Chien JT, Lin CH, et al. Fracture liaison services improve outcomes of patients with osteoporosis-related fractures: A systematic literature review and meta-analysis. Bone. Jun 2018;111:92-100. Epub 2018/03/21.

157. Axelsson KF, Johansson H, Lundh D, Moller M, Lorentzon M. Association Between Recurrent Fracture Risk and Implementation of Fracture Liaison Services in Four Swedish Hospitals: A Cohort Study. J Bone Miner Res. Jul 2020;35(7):1216-23. Epub 2020/02/26.

158. McLellan AR, Wolowacz SE, Zimovetz EA, Beard SM, Lock S, McCrink L, et al. Fracture liaison services for the evaluation and management of patients with osteoporotic fracture: a cost-effectiveness evaluation based on data collected over 8 years of service provision. Osteoporos Int. Jul 2011;22(7):2083-98. Epub 2011/05/25.

159. Lorentzon M. Treating osteoporosis to prevent fractures: current concepts and future developments. J Intern Med. Apr 2019;285(4):381-94. Epub 2019/01/19.

160. Fontalis A, Kenanidis E, Kotronias RA, Papachristou A, Anagnostis P, Potoupnis M, et al. Current and emerging osteoporosis pharmacotherapy for women: state of the art therapies for preventing bone loss. Expert Opin Pharmacother. Jun 2019;20(9):1123-34.

161. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc. Sep 2008;83(9):1032-45. Epub 2008/09/09.

162. Grey A, Bolland MJ, Horne A, Wattie D, House M, Gamble G, et al. Five years of anti-resorptive activity after a single dose of zoledronate--results from a randomized double-blind placebo-controlled trial. Bone. Jun 2012;50(6):1389-93. Epub 2012/04/03.

163. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. Osteoporos Int. Oct 2014;25(10):2359-81. Epub 2014/09/04.

164. Kanis JA, Cooper C, Rizzoli R, Reginster JY, Scientific Advisory Board of the European Society for C, Economic Aspects of O, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. Jan 2019;30(1):3-44. Epub 2018/10/17.

165. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA. Oct 13 1999;282(14):1344-52. Epub 1999/10/20.

166. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, et al. Fracture risk reduction with alendronate in women with osteoporosis: the Fracture Intervention Trial. FIT Research Group. J Clin Endocrinol Metab. Nov 2000;85(11):4118-24. Epub 2000/11/30.

167. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med. May 3 2007;356(18):1809-22. Epub 2007/05/04.

168. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. Aug 20 2009;361(8):756-65. Epub 2009/08/13.

169. Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol. Jul 2017;5(7):513-23. Epub 2017/05/27.

170. Tsourdi E, Langdahl B, Cohen-Solal M, Aubry-Rozier B, Eriksen EF, Guanabens N, et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. Bone. Dec 2017;105:11-7. Epub 2017/08/10.

171. Noble JA, McKenna MJ, Crowley RK. Should denosumab treatment for osteoporosis be continued indefinitely? Ther Adv Endocrinol Metab. 2021;12:20420188211010052. Epub 2021/06/10.

172. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med. May 10 2001;344(19):1434-41. Epub 2001/05/11.

173. Kendler DL, Marin F, Zerbini CAF, Russo LA, Greenspan SL, Zikan V, et al. Effects of teriparatide and risedronate on new fractures in post-menopausal women with severe osteoporosis (VERO): a multicentre, double-blind, double-dummy, randomised controlled trial. Lancet. Jan 20 2018;391(10117):230-40. Epub 2017/11/14.

174. Socialstyrelsen. Nationella riktlinjer Målnivåer – vård vid rörelseorganens sjukdomar Målnivåer för indikatorer. 2021.

175. McClung MR, Grauer A, Boonen S, Bolognese MA, Brown JP, Diez-Perez A, et al. Romosozumab in postmenopausal women with low bone mineral density. N Engl J Med. Jan 30 2014;370(5):412-20. Epub 2014/01/03.

176. Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab Treatment in Postmenopausal Women with Osteoporosis. N Engl J Med. Oct 20 2016;375(16):1532-43. Epub 2016/11/01.

177. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. N Engl J Med. Oct 12 2017;377(15):1417-27. Epub 2017/09/12.

178. Cosman F, Nieves JW, Dempster DW. Treatment Sequence Matters: Anabolic and Antiresorptive Therapy for Osteoporosis. J Bone Miner Res. Feb 2017;32(2):198-202. Epub 2016/12/08.

179. Leder BZ, Neer RM, Wyland JJ, Lee HW, Burnett-Bowie SM, Finkelstein JS. Effects of teriparatide treatment and discontinuation in postmenopausal women and eugonadal men with osteoporosis. J Clin Endocrinol Metab. Aug 2009;94(8):2915-21. Epub 2009/05/14.

180. Pouilles JM, Tremollieres F, Ribot C. Variability of vertebral and femoral postmenopausal bone loss: a longitudinal study. Osteoporos Int. 1996;6(4):320-4. Epub 1996/01/01.

181. Bone HG, Cosman F, Miller PD, Williams GC, Hattersley G, Hu MY, et al. ACTIVExtend: 24 Months of Alendronate After 18 Months of Abaloparatide or Placebo for Postmenopausal Osteoporosis. J Clin Endocrinol Metab. Aug 1 2018;103(8):2949-57. Epub 2018/05/26.

182. Leder BZ, Tsai JN, Uihlein AV, Wallace PM, Lee H, Neer RM, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomised controlled trial. Lancet. Sep 19 2015;386(9999):1147-55. Epub 2015/07/07.

183. Langdahl B. Treatment of postmenopausal osteoporosis with bone-forming and antiresorptive treatments: Combined and sequential approaches. Bone. Oct 2020;139:115516. Epub 2020/07/06.

184. Harvey NC, Biver E, Kaufman JM, Bauer J, Branco J, Brandi ML, et al. The role of calcium supplementation in healthy musculoskeletal ageing : An expert consensus meeting of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases

(ESCEO) and the International Foundation for Osteoporosis (IOF). Osteoporos Int. Feb 2017;28(2):447-62. Epub 2016/10/21.

185. Guralnik JM, Branch LG, Cummings SR, Curb JD. Physical performance measures in aging research. J Gerontol. Sep 1989;44(5):M141-6. Epub 1989/09/01.

186. Jette AM, Jette DU, Ng J, Plotkin DJ, Bach MA. Are performance-based measures sufficiently reliable for use in multicenter trials? Musculoskeletal Impairment (MSI) Study Group. J Gerontol A Biol Sci Med Sci. Jan 1999;54(1):M3-6. Epub 1999/02/23.

187. Giorgetti MM, Harris BA, Jette A. Reliability of clinical balance outcome measures in the elderly. Physiother Res Int. 1998;3(4):274-83.

188. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc. Feb 1991;39(2):142-8.

189. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport. Jun 1999;70(2):113-9.

190. Montero-Odasso M, Schapira M, Soriano ER, Varela M, Kaplan R, Camera LA, et al. Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. J Gerontol A Biol Sci Med Sci. Oct 2005;60(10):1304-9.

191. Bohannon RW. Hand-grip dynamometry predicts future outcomes in aging adults. J Geriatr Phys Ther. 2008;31(1):3-10. Epub 2008/05/21.

192. Michikawa T, Nishiwaki Y, Takebayashi T, Toyama Y. One-leg standing test for elderly populations. J Orthop Sci. Sep 2009;14(5):675-85.

193. Bohannon RW. Reference values for the timed up and go test: a descriptive meta-analysis. J Geriatr Phys Ther. 2006;29(2):64-8. Epub 2006/08/18.

194. Nakazono T, Kamide N, Ando M. The Reference Values for the Chair Stand Test in Healthy Japanese Older People: Determination by Meta-analysis. J Phys Ther Sci. Nov 2014;26(11):1729-31. Epub 2014/12/02.

195. Graham JE, Ostir GV, Fisher SR, Ottenbacher KJ. Assessing walking speed in clinical research: a systematic review. J Eval Clin Pract. Aug 2008;14(4):552-62. Epub 2008/05/09.

196. Orwoll E, Blank JB, Barrett-Connor E, Cauley J, Cummings S, Ensrud K, et al. Design and baseline characteristics of the osteoporotic fractures in men (MrOS) study--a large observational study of the determinants of fracture in older men. Contemp Clin Trials. Oct 2005;26(5):569-85. Epub 2005/08/09.

197. Johansson H, Oden A, Kanis J, McCloskey E, Lorentzon M, Ljunggren O, et al. Low bone mineral density is associated with increased mortality in elderly men: MrOS Sweden. Osteoporos Int. May 2011;22(5):1411-8. Epub 2010/06/30.

198. Angbratt M, Moller M. Questionnaire about calcium intake: can we trust the answers? Osteoporos Int. 1999;9(3):220-5.

199. Washburn RA, Smith KW, Jette AM, Janney CA. The Physical Activity Scale for the Elderly (PASE): development and evaluation. J Clin Epidemiol. Feb 1993;46(2):153-62.

200. Ware J, Jr., Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. Med Care. Mar 1996;34(3):220-33.

201. MacNeil JA, Boyd SK. Improved reproducibility of high-resolution peripheral quantitative computed tomography for measurement of bone quality. Med Eng Phys. Jul 2008;30(6):792-9.

202. Sundh D, Rudang R, Zoulakis M, Nilsson AG, Darelid A, Lorentzon M. A High Amount of Local Adipose Tissue Is Associated With High Cortical Porosity and Low Bone Material Strength in Older Women. J Bone Miner Res. Apr 2016;31(4):749-57.

203. Burghardt AJ, Buie HR, Laib A, Majumdar S, Boyd SK. Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT. Bone. Sep 2010;47(3):519-28.

204. Nilsson AG, Sundh D, Johansson L, Nilsson M, Mellstrom D, Rudang R, et al. Type 2 Diabetes Mellitus Is Associated With Better Bone Microarchitecture But Lower Bone Material Strength and Poorer Physical Function in Elderly Women: A Population-Based Study. J Bone Miner Res. May 2017;32(5):1062-71. Epub 2016/12/13.

205. Wolf SL, Catlin PA, Gage K, Gurucharri K, Robertson R, Stephen K. Establishing the reliability and validity of measurements of walking time using the Emory Functional Ambulation Profile. Phys Ther. Dec 1999;79(12):1122-33.

206. Peolsson A, Hedlund R, Oberg B. Intra- and inter-tester reliability and reference values for hand strength. J Rehabil Med. Jan 2001;33(1):36-41.

207. Mackey DC, Lui LY, Cawthon PM, Bauer DC, Nevitt MC, Cauley JA, et al. High-trauma fractures and low bone mineral density in older women and men. JAMA. Nov 28 2007;298(20):2381-8.

208. Miller ML, Wang MC. Accuracy of ICD-9-CM coding of cervical spine fractures: implications for research using administrative databases. Ann Adv Automot Med. Oct 2008;52:101-5.

209. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. Jun 9 2011;11:450. Epub 2011/06/11.

210. Katz MH. Multivariable analysis: a primer for readers of medical research. Ann Intern Med. Apr 15 2003;138(8):644-50. Epub 2003/04/16.

211. McHugh ML. Interrater reliability: the kappa statistic. Biochem Med (Zagreb). 2012;22(3):276-82. Epub 2012/10/25.

212. Sornay-Rendu E, Boutroy S, Munoz F, Delmas PD. Alterations of cortical and trabecular architecture are associated with fractures in postmenopausal women, partially independent of decreased BMD measured by DXA: the OFELY study. J Bone Miner Res. Mar 2007;22(3):425-33.

213. Sornay-Rendu E, Cabrera-Bravo JL, Boutroy S, Munoz F, Delmas PD. Severity of vertebral fractures is associated with alterations of cortical architecture in postmenopausal women. J Bone Miner Res. Apr 2009;24(4):737-43.

214. Stein EM, Liu XS, Nickolas TL, Cohen A, McMahon DJ, Zhou B, et al. Microarchitectural abnormalities are more severe in postmenopausal women with vertebral compared to nonvertebral fractures. J Clin Endocrinol Metab. Oct 2012;97(10):E1918-26. Epub 2012/07/24.

215. Leslie WD, Lix LM, Tsang JF, Caetano PA, Manitoba Bone Density P. Single-site vs multisite bone density measurement for fracture prediction. Arch Intern Med. Aug 13-27 2007;167(15):1641-7.

216. Grampp S, Lang P, Jergas M, Gluer CC, Mathur A, Engelke K, et al. Assessment of the skeletal status by peripheral quantitative computed tomography of the forearm: short-term precision in vivo and comparison to dual X-ray absorptiometry. J Bone Miner Res. Oct 1995;10(10):1566-76. Epub 1995/10/01.

217. Melton LJ, 3rd, Riggs BL, Keaveny TM, Achenbach SJ, Hoffmann PF, Camp JJ, et al. Structural determinants of vertebral fracture risk. J Bone Miner Res. Dec 2007;22(12):1885-92.

218. Sundh D, Mellstrom D, Nilsson M, Karlsson M, Ohlsson C, Lorentzon M. Increased Cortical Porosity in Older Men With Fracture. J Bone Miner Res. Sep 2015;30(9):1692-700.

219. Sundh D, Nilsson AG, Nilsson M, Johansson L, Mellstrom D, Lorentzon M. Increased cortical porosity in women with hip fracture. J Intern Med. May 2017;281(5):496-506.

220. Morris R, Harwood RH, Baker R, Sahota O, Armstrong S, Masud T. A comparison of different balance tests in the prediction of falls in older women with vertebral fractures: a cohort study. Age Ageing. Jan 2007;36(1):78-83.

221. Larsson BAM, Johansson L, Johansson H, Axelsson KF, Harvey N, Vandenput L, et al. The timed up and go test predicts fracture risk in older women independently of clinical risk factors and bone mineral density. Osteoporos Int. Jan 2021;32(1):75-84. Epub 2020/10/23.

222. Larsson BAM, Johansson L, Mellstrom D, Johansson H, Axelsson KF, Harvey N, et al. One leg standing time predicts fracture risk in older women independent of clinical risk factors and BMD. Osteoporos Int. Jan 2022;33(1):185-94. Epub 2021/09/10.

223. Diaz-Arribas MJ, Fernandez-Serrano M, Royuela A, Kovacs FM, Gallego-Izquierdo T, Ramos-Sanchez M, et al. Minimal Clinically Important Difference in Quality of Life for Patients with Low Back Pain. Spine (Phila Pa 1976). Jun 27 2017.

224. Sanfelix-Genoves J, Hurtado I, Sanfelix-Gimeno G, Reig-Molla B, Peiro S. Impact of osteoporosis and vertebral fractures on quality-of-life. a population-based study in Valencia, Spain (The FRAVO Study). Health Qual Life Outcomes. Apr 06 2011;9:20.

225. Roux C, Fechtenbaum J, Kolta S, Briot K, Girard M. Mild prevalent and incident vertebral fractures are risk factors for new fractures. Osteoporos Int. Dec 2007;18(12):1617-24.

226. Johansson H, Oden A, McCloskey EV, Kanis JA. Mild morphometric vertebral fractures predict vertebral fractures but not non-vertebral fractures. Osteoporos Int. Jan 2014;25(1):235-41.

227. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. Study of Osteoporotic Fractures Research Group. J Bone Miner Res. May 1999;14(5):821-8.

228. Delmas PD, Genant HK, Crans GG, Stock JL, Wong M, Siris E, et al. Severity of prevalent vertebral fractures and the risk of subsequent vertebral and nonvertebral fractures: results from the MORE trial. Bone. Oct 2003;33(4):522-32.

229. Prince RL, Lewis JR, Lim WH, Wong G, Wilson KE, Khoo BC, et al. Adding Lateral Spine Imaging for Vertebral Fractures to Densitometric Screening: Improving Ascertainment of Patients at High Risk of Incident Osteoporotic Fractures. J Bone Miner Res. Feb 2019;34(2):282-9.

230. Fuerst T, Wu C, Genant HK, von Ingersleben G, Chen Y, Johnston C, et al. Evaluation of vertebral fracture assessment by dual X-ray absorptiometry in a multicenter setting. Osteoporos Int. Jul 2009;20(7):1199-205.

231. Domiciano DS, Figueiredo CP, Lopes JB, Kuroishi ME, Takayama L, Caparbo VF, et al. Vertebral fracture assessment by dual X-ray absorptiometry: a valid tool to detect vertebral fractures in community-dwelling older adults in a population-based survey. Arthritis Care Res (Hoboken). May 2013;65(5):809-15.

232. Aubry-Rozier B, Fabreguet I, Iglesias K, Lamy O, Hans D. Impact of level of expertise versus the statistical tool on vertebral fracture assessment (VFA) readings in cohort studies. Osteoporos Int. Feb 2017;28(2):523-7. Epub 2016/09/04.

233. Borges JLC, Sousa da Silva M, Ward RJ, Diemer KM, Yeap SS, Lewiecki EM. Repeating Vertebral Fracture Assessment: 2019 ISCD Official Position. J Clin Densitom. Oct - Dec 2019;22(4):484-8. Epub 2019/08/04.

234. Lems WF, Paccou J, Zhang J, Fuggle NR, Chandran M, Harvey NC, et al. Vertebral fracture: epidemiology, impact and use of DXA vertebral fracture assessment in fracture liaison services. Osteoporos Int. Mar 2021;32(3):399-411. Epub 2021/01/22.

235. Schousboe JT, Lix LM, Morin SN, Derkatch S, Bryanton M, Alhrbi M, et al. Vertebral Fracture Assessment Increases Use of Pharmacologic Therapy for Fracture Prevention in Clinical Practice. J Bone Miner Res. Dec 2019;34(12):2205-12. Epub 2019/08/02.

236. Reniu AC, Ong T, Ajmal S, Sahota O. Vertebral fracture assessment in patients presenting with a non-hip non-vertebral fragility fracture: experience of a UK Fracture Liaison Service. Arch Osteoporos. Dec 2017;12(1):23. Epub 2017/03/02.

237. kunskapsstyrning Nsf, sjukvård H-o, samverkan Sri. Konsekvensbeskrivning för personcentrerat och sammanhållet vårdförlopp Osteoporos - sekundärprevention efter fraktur. 2021.

238. Kanis JA, Johnell O. Requirements for DXA for the management of osteoporosis in Europe. Osteoporos Int. Mar 2005;16(3):229-38. Epub 2004/12/25.

239. Kanis JA, Harvey NC, Cooper C, Johansson H, Oden A, McCloskey EV, et al. A systematic review of intervention thresholds based on FRAX : A report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. Arch Osteoporos. Dec 2016;11(1):25. Epub 2016/07/29.

240. Kanis JA, Harvey NC, McCloskey E, Bruyere O, Veronese N, Lorentzon M, et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. Osteoporos Int. Jan 2020;31(1):1-12. Epub 2019/11/14.

241. Curtis JR, Arora T, Matthews RS, Taylor A, Becker DJ, Colon-Emeric C, et al. Is withholding osteoporosis medication after fracture sometimes rational? A comparison of the risk for second fracture versus death. J Am Med Dir Assoc. Oct 2010;11(8):584-91. Epub 2010/10/05.

242. Axelsson KF, Wallander M, Johansson H, Lundh D, Lorentzon M. Hip fracture risk and safety with alendronate treatment in the oldest-old. J Intern Med. Dec 2017;282(6):546-59. Epub 2017/09/01.

243. Soreskog E, Lindberg I, Kanis JA, Akesson KE, Willems D, Lorentzon M, et al. Cost-effectiveness of romosozumab for the treatment of postmenopausal women with severe osteoporosis at high risk of fracture in Sweden. Osteoporos Int. Mar 2021;32(3):585-94. Epub 2021/01/08.

244. Ismail AA, O'Neill TW, Cooper C, Finn JD, Bhalla AK, Cannata JB, et al. Mortality associated with vertebral deformity in men and women: results from the European Prospective Osteoporosis Study (EPOS). Osteoporos Int. 1998;8(3):291-7. Epub 1998/11/03.

245. Kanis JA, Oden A, Johnell O, De Laet C, Jonsson B. Excess mortality after hospitalisation for vertebral fracture. Osteoporos Int. Feb 2004;15(2):108-12. Epub 2003/11/05.

246. Lespessailles E, Ibrahim-Nasser N, Toumi H, Chapurlat R. Contribution of high resolution peripheral quantitative CT to the management of bone and joint diseases. Joint Bone Spine. May 2018;85(3):301-6. Epub 2017/05/18.

247. Biver E, Durosier-Izart C, Chevalley T, van Rietbergen B, Rizzoli R, Ferrari S. Evaluation of Radius Microstructure and Areal Bone Mineral Density Improves Fracture Prediction in Postmenopausal Women. J Bone Miner Res. Feb 2018;33(2):328-37. Epub 2017/09/30.

248. Sornay-Rendu E, Boutroy S, Duboeuf F, Chapurlat RD. Bone Microarchitecture Assessed by HR-pQCT as Predictor of Fracture Risk in Postmenopausal Women: The OFELY Study. J Bone Miner Res. Jun 2017;32(6):1243-51. Epub 2017/03/10.

249. Ohlsson C, Sundh D, Wallerek A, Nilsson M, Karlsson M, Johansson H, et al. Cortical Bone Area Predicts Incident Fractures Independently of Areal Bone Mineral Density in Older Men. J Clin Endocrinol Metab. Feb 1 2017;102(2):516-24. Epub 2016/11/23.

250. Tome-Bermejo F, Pinera AR, Alvarez L. Osteoporosis and the Management of Spinal Degenerative Disease (II). Arch Bone Jt Surg. Nov 2017;5(6):363-74.

251. Aebi M. The adult scoliosis. Eur Spine J. Dec 2005;14(10):925-48. Epub 2005/12/06.

252. Bradford DS, Tay BK, Hu SS. Adult scoliosis: surgical indications, operative management, complications, and outcomes. Spine (Phila Pa 1976). Dec 15 1999;24(24):2617-29. Epub 2000/01/15.

253. Taylor HJ, Harding I, Hutchinson J, Nelson I, Blom A, Tobias JH, et al. Identifying scoliosis in population-based cohorts: development and validation of a novel method based on total-body dual-energy x-ray absorptiometric scans. Calcif Tissue Int. Jun 2013;92(6):539-47. Epub 2013/03/05.

254. Jamaludin A, Fairbank J, Harding I, Kadir T, Peters TJ, Zisserman A, et al. Identifying Scoliosis in Population-Based Cohorts: Automation of a Validated Method Based on Total Body Dual Energy X-ray Absorptiometry Scans. Calcif Tissue Int. Apr 2020;106(4):378-85. Epub 2020/01/11.