

Physical activity, bone density, and fragility fractures in women

Undis Englund



Department of Community Medicine and Rehabilitation,
Geriatric Medicine
Department of Pharmacology and Clinical Neuroscience,
Clinical Pharmacology
901 87 Umeå
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*To my family,
especially my father in memoriam*

Table of Contents

Table of Contents	5
Abbreviations	7
List of papers	9
Sammanfattning på svenska	10
Abstract	13
Introduction	16
Bone structure	18
Bone matrix	18
Bone cells	19
Bone turnover	21
Biochemical markers of bone metabolism	23
Bone formation	23
Osteocalcin	23
Bone-specific alkaline phosphatase	24
Procollagen 1 extension peptides	24
Bone resorption	25
C-telopeptide of collagen cross-links	25
N-telopeptide of collagen cross-links (NTx)	26
Collagen pyridinium crosslinks	26
Acid phosphatase	26
Bone measurements	27
Dual energy X-ray Absorptiometry	27
Peripheral DXA	30
Single X-ray absorptiometry	31
Quantitative computerized tomography	31
Peripheral quantitative computerized tomography	31
Quantitative ultrasound	32
Lifetime changes in bone mass	33
Osteoporosis	35
Diagnostic criteria	36
Fractures	38
Wrist fracture	38
Vertebral compression fracture	39
Hip fracture	41
Risk factors for osteoporosis and fragility fractures	43
Physical activity	45
The influence on bone mass	45

The influence of physical activity on neuromuscular function, falls, and fracture risk	48
Vitamin D, balance, muscle strength, and fracture risk	51
Rationale for the thesis	52
Aims and hypotheses of the thesis	53
Materials and methods	54
Study I and II	54
Subjects	54
Assessments	56
Intervention	57
Study III and IV	58
Subjects	58
Assessments	58
Statistics	60
Study I	60
Study II	61
Study III and IV	61
Ethics	62
Summary of results	63
Study I	63
A 1-year combined weight-bearing training programme is beneficial for bone mineral density and neuromuscular function in older women	63
Study II	64
The beneficial effects of exercise on BMD are lost after cessation: a 5-year follow-up in older post-menopausal women	64
Study III	66
Physical activity in middle-aged women and hip fracture risk – the UFO study	66
Study IV	66
Active commuting reduces the risk of wrist fractures in middle-aged women – the UFO study	66
General discussion	68
Strength and limitations of the studies	77
Ethical considerations	79
Clinical implications	80
Implications for future research	81
Conclusions	82
Acknowledgements	83
References	86

Abbreviations

1,25(OH) ₂ D	1,25-hydroxy Vitamin D
25(OH)D	25-hydroxy Vitamin D
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BMU	Basic multicellular units
BSAP	Bone specific alkaline phosphatase
BUA	Broadband ultrasound attenuation
CI	Confidence interval
CTx	C-telopeptide of collagen cross-links
CV	Coefficient of variation
DPD	Deoxypyridinoline
DXA	Dual energy X-ray absorptiometry
pDXA	peripheral Dual energy X-ray absorptiometry
HRT	Hormone replacement therapy
NTx	N-telopeptide of collagen cross-links
OC	Osteocalcin
OPG	Osteoprotegerin
OR	Odds ratio
P1CP	Carboxyterminal propeptide of type I collagen
P1NP	Aminoterminal propeptide of type I collagen
PBM	Peak bone mass

PTH	Parathyroid hormone
PYD	Pyridinoline
QALY	Quality adjusted life year
QCT	Quantitative computerized tomography
pQCT	Peripheral quantitative computerized tomography
QUS	Quantitative ultrasound
RANK	Receptor activator of nuclear factor kappaß
RANKL	Receptor activator of nuclear factor kappaß ligand
SD	Standard deviation
SEK	Swedish crowns
SOS	Speed of sound
SXA	Single X-ray absorptiometry
TRACP5b	Tartrate-resistant acid phosphatase 5b
UFO	Umeå fracture and osteoporosis
VFA	Vertebral fracture assessment
VHU	Västerbottens hälsoundersökningar
WHO	World Health Organization

List of papers

I. Englund U, Littbrand H, Sundell A, Pettersson U, Bucht G. A one-year combined weight-bearing training program is beneficial for bone mineral density and neuromuscular function in older women. *Osteoporos Int* 2005 Sep; 16(9): 1117-1123.

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Sammanfattning på svenska

Svenska och norska kvinnor har flest höftfrakturer i världen. Bakomliggande orsaker är ofullständigt kända. Ärftlighet, brist på solljus och därmed D-vitamin under vinterhalvåret, tillsammans med livsstilsfaktorer såsom bl.a. fysisk inaktivitet och rökning är möjliga orsaker till benskörhet och frakturer. Risken att drabbas av en benskörhetsfraktur ökar med åldern och livstidsrisken för en 50-årig kvinna är ca 46 %. Fysisk aktivitet har i studier på yngre individer visat sig stimulera benmassan och motverka benskörhet.

Ett syfte med den här avhandlingen har varit att studera effekten av fysisk aktivitet på bentäthet, muskelstyrka och

balans hos äldre kvinnor. En grupp frivilliga kvinnor med en medelålder på 73 år lottades till antingen träningsgrupp (24 st.) eller kontrollgrupp (24 st.). Träningsgruppen utförde ett viktbärande träningsprogram under 50 minuter, två gånger per vecka, under ledning av sjukgymnast, medan kontrollgruppen fortsatte att leva som vanligt. Efter tolv månader hade träningsgruppen ökad bentäthet i höften samt förbättrad muskelstyrka och ökad gånghastighet, jämfört med kontrollgruppen. 21 kvinnor från träningsgruppen respektive 19 från kontrollgruppen deltog i 12-månadersuppföljningen. Vid uppföljning fem år senare när försökspersonerna var i genomsnitt 79 år gamla hade träningseffekterna försvunnit och det var inte längre någon skillnad

mellan träningsgrupp (18 st.) och kontrollgrupp (16 st.).

Ett annat syfte har varit att studera samband mellan fysisk aktivitet i medelåldern och framtida risk för höftfraktur och handledsfraktur. För dessa studier har vi använt oss av kvinnor som deltagit i Västerbottens hälsoundersökningar (VHU), en longitudinell hälsoundersökning som erbjuds alla 40-, 50- och 60-åringar i Västerbottens län. I VHU svarar deltagarna på en omfattande enkät med livsstilsfrågor innefattande även fysisk aktivitet. Ur VHU-materialet har valts ut kvinnor som drabbats av höftfraktur (81 st.) eller handledsfraktur (376 st.) och som svarat på livsstilsenkäten innan de fick sin fraktur. Därefter har åldersmatchade kontroller utan fraktur valts ut ur samma

material. Logistisk regressionsanalys visade att fritidsaktiviteter såsom bär- och svampplockning sänkte risken för att drabbas av en höftfraktur med 76 % jämfört med inaktivitet. Risken för handledsfraktur minskade med 52 % för dem som i hög utsträckning cyklade och promenerade till arbetet jämfört med dem som använde bil eller buss. Även aktiviteter såsom snöskottning och dans på fritiden bidrog till minskad risk för handledsfraktur.

Sammanfattningsvis tyder resultaten på att träning för att förbättra bentäthet, muskelstyrka och gångförmåga lönar sig även i hög ålder, men att effekterna försvinner när man slutar träna. Resultaten talar även för att en aktiv livsstil i medelåldern minskar risken för framtida höft-

och handledsfraktur. Mekanismer
kan tänkas vara förbättrad
muskelstyrka och balans hos de

fysiskt aktiva vilket bidrar till att
förhindra fall, men även en möjlig
positiv effekt direkt på skelettet.

Abstract

Scandinavia has among the highest incidence of fragility fractures in the world. The reasons for this are unknown, but might involve differences in genetic and/or environmental factors, such as sunlight exposure and levels of physical activity. Weight-bearing exercise is thought to have a beneficial effect on bone health in the young, but few studies have evaluated whether exercise in older subjects affects bone density and protects against fragility fractures.

The initial objective of this thesis was to evaluate whether a combined weight-bearing training programme twice a week would be beneficial as regards bone mineral density (BMD) and neuromuscular function in older women. Forty-eight community

living women with a mean age of 73 years were recruited for this 12-month prospective, randomised controlled trial, and were randomly assigned to an intervention group (n=24) or a control group (n=24). The intervention group displayed significant increments in BMD at the Ward's triangle, maximum walking speed, and isometric grip strength compared to the control group. The second objective was to investigate if training effects were retained in older women five years after the cessation of training. The 40 women who completed the first study included in this thesis were invited to take part in a follow-up assessment five years later, and 34 women (~79 years) agreed to participate. During these five years both groups had sustained significant losses in hip BMD and in all

neuromuscular function tests, and the previous exercise-induced intergroup differences were no longer seen.

The third and fourth objective of this thesis was to investigate whether exercise and weight-bearing leisure activities in middle-aged women are associated with a decreased risk of sustaining hip or wrist fractures at a later stage. A cohort of women participating in the Umeå Fracture and Osteoporosis (UFO) study, a longitudinal, nested case-control study investigating associations between bone markers, lifestyle, and osteoporotic fractures, was used for the purpose of this investigation. Eighty-one hip fracture cases and 376 wrist fracture cases, which had reported lifestyle data before they sustained their fracture, were

identified. These cases were compared with age-matched controls identified from the same cohort. Using conditional logistic regression analysis with adjustments for height, BMI, smoking, and menopausal status, results showed that moderate frequency of leisure physical activities such as gardening and berry/mushroom picking, were associated with reduced hip fracture risk (OR 0.28; 95% CI 0.12 – 0.67), whereas active commuting (especially walking) along with dancing and snow shoveling in leisure time, reduced the wrist fracture risk (OR 0.48; 95% CI 0.27 – 0.88, OR 0.42; 95% CI 0.22 – 0.80 and OR 0.50; 95% CI 0.32 – 0.79 respectively).

In summary, this thesis suggests that weight-bearing physical activity is beneficial for BMD and

neuromuscular functions such as muscle strength and gait in older women, and that a physically active lifestyle, with outdoor activities, in middle age is associated with reduced risk of both hip and wrist fractures. Possible mechanisms underlying this association include improved muscle strength, coordination,

and balance, resulting in a decreased risk of falling and perhaps also direct skeletal benefits.

Keywords: physical activity, bone density, neuromuscular function, fragility fractures, women

Introduction

Several epidemiological studies have indicated an increasing incidence of osteoporotic fractures in Europe and North America during the past 30–40 years [1-3], although some reports indicate a slowdown in the hip fracture incidence trend, especially for women [4-6]. Nevertheless, large cohorts of older people who are vulnerable to fractures will most probably result in an overall rising number of fractures [7]. Sweden is among the countries most affected by fragility fractures in the world [3, 8, 9] and the reasons for this are largely unknown, but genetic and environmental factors, including levels of physical activity, are thought to contribute to the incidence of osteoporosis and fragility fractures [10].

The adverse impact of osteoporosis lies in associated fractures, which cause great suffering, increased mortality, and reduced quality of life for those who live with the disease [11-13]. The total number of fragility fractures in Sweden is about 70,000 per year in a population of 9.3 million [14, 15], and the lifetime risk for a 50-year-old Swedish woman to sustain a fragility fracture is 46% [16]. For a 50-year-old Swedish man, the lifetime risk of sustaining a fragility fracture is 22%. Fractures are associated with high costs for society, and were estimated at 5.6 billion SEK in 2005, which is about 3.2% of the total health care costs in Sweden. Medical care accounted for 31% of these costs and community care accounted for approximately 66%. Remaining costs were made up of

informal care (2%) and indirect costs (1%). These costs combined with the annual value of quality-adjusted life-years (QALYs) lost resulted in a total annual societal burden of osteoporosis in Sweden at an estimated 15.2 billion SEK in 2005. Assuming no changes in the age-differentiated fracture risk, the annual burden of osteoporosis is estimated to reach 26.3 billion SEK in the year 2050 [17]. Physical activity has a beneficial

effect on bone mineral density (BMD), but even though osteoporotic fractures constitute a major problem that increases with age, most studies on the influence of physical activity on bone mass and fracture risk have been performed in younger men and women. In this thesis the purpose was to focus on physical activity and BMD as risk factors for fragility fractures among middle-aged and older women.

Bone structure

The skeleton consists of two types of bone tissue, i.e. cortical (compact) bone, which makes up 80% of adult bone, and trabecular (cancellous) bone, which makes up 20% of the bone mass and is the most metabolically active bone type. Cortical bone is dense and arranged concentrically around central Haversian canals. Trabecular bone consists of interconnecting trabecular plates and rods, orientated along lines of stress. The arrangement of the trabecular plates confers an adequate amount of rigidity to the cortical shell and allows bone to resist compressive and torsional forces, giving the bone maximum strength. At a microscopic level, bone tissue consists of an organic matrix within which bone mineral is deposited and bone cells

arranged in basic multicellular units (BMUs), which are engaged in the process of bone remodelling [18].

Bone matrix

The organic bone matrix consists predominantly of type 1 collagen, which represents more than 90% of the matrix components. Other components of the bone matrix include glycoproteins, proteoglycans, osteocalcin, and osteonectin. Each unit of collagen is formed as procollagen within the osteoblast and the amino- and carboxy-terminals of procollagen are enzymatically cleaved outside the cell. Two alpha-1 chains and one alpha-2 chain are twisted together and the formation of cross-links results in the triple helix collagen molecule, the type 1 collagen. The type and amount of cross-linking influence

mineralization and bone strength [19]. Mineral crystals are deposited within the matrix mainly in the form of hydroxyapatite $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$. The bone matrix also contains trace elements as Ba, Br, Fe, Sr, and Zn [20].

Bone cells

There are three main cell types in bone, i.e. osteoblasts, osteoclasts, and osteocytes.

Osteoblasts are derived from pluripotent stromal stem cells, synthesize bone matrix, and are involved in the subsequent mineralization. Osteoblasts also act like endocrine cells, interacting with glucose and fat metabolism [21-23]. When involved in bone formation, osteoblasts appear as cuboidal cells in close connection to the

newly formed unmineralised bone, called osteoid. Some die by the process of apoptosis, while others are buried within mineralized bone to become osteocytes or lining cells covering the bone surfaces.

Osteocytes are small flattened cells within bone matrix that are connected to one another and to lining cells on the bone surface. In cortical bone, osteocytes are arranged circumferentially around the concentric bone lamellae, whereas in cancellous bone they lie parallel to the axis of the collagen fibres. Osteocytes are derived from osteoblasts and play an important role in the osteogenic response to mechanical stimuli, 'sensing' physical strains and initiating an appropriate modelling or remodelling response via the

production of a cascade of chemical messengers. The life span of osteocytes is critically dependent on, and inversely related to, bone turnover. Osteocytes are terminally differentiated cells and undergo apoptosis or are phagocytosed by osteoclasts during bone resorption.

Osteoclasts are large multinucleated cells that are derived from hematopoietic precursors of the monocyte-macrophage lineage. They perform the function of resorption

of mineralized vital bone. Osteoclasts are formed by fusion of mononuclear cells and are characterized by the presence of a ruffled border. During the process of resorption, hydrogen ions that dissolve bone mineral are pumped through the ruffled border by a proton pump. Lysosomal enzymes, including cysteine proteinases, are then released to degrade bone matrix [24] Osteoclasts undergo apoptosis after a cycle of resorption, a process favoured by estrogens [25].

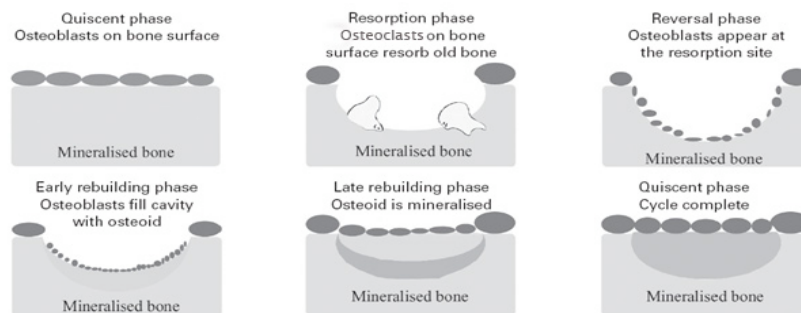


Fig. 1. Bone remodeling at a bone multicellular unit (BMU). Kindly provided by dr A. Nordström.

Bone turnover

Around one million BMUs operate at any given time and remodel both cortical and cancellous bone. Old bone is removed by the osteoclasts and replaced by the osteoblasts. There is strong coupling between the osteoblastic and osteoclastic processes. The differentiation, activation, and survival of osteoclasts are dependent on the receptor activator of nuclear factor kappaB (RANK). The RANK ligand (RANKL), which is produced by the osteoblast, binds to the RANK for differentiation and activation of osteoclasts and its precursors. Osteoclast differentiation can be inhibited by osteoprotegerin (OPG), also produced by osteoblasts, which binds competitively to RANKL, thereby preventing interaction with

RANK. RANKL and its two receptors RANK and OPG are thus key regulators of osteoclast-mediated bone resorption and bone turnover [19, 26]. Local factors such as physical strains as well as systemic hormones along with cytokines also influence the remodelling process. Parathyroid hormone (PTH) vitamin D (1,25(OH)₂D) and calcitonin are involved in the calcium homeostasis in serum and acts directly on both osteoblasts and osteoclasts. Prostaglandins and leukotrienes are inflammatory mediators that stimulate the osteoclasts. Thyroid hormones enhance the rate of remodelling [25, 27]. The effects of estrogens on bone are mediated through reduced osteoclast numbers as a result of reduced production of proresorptive cytokines as

RANKL. Testosterone has an effect on bone in males, mediated via the androgen receptor, but estrogens also play an important role in skeletal homeostasis in men [24]. The resorptive phase of the remodelling process has been estimated to last about ten days, and the complete remodelling

cycle at each microscopic site takes around three to six months [25]). In adults, about 10% of the bone is replaced in one year [28]. Under normal circumstances the sequence of resorption is followed by formation and there is a balance between the amounts of bone resorbed and formed.

Biochemical markers of bone metabolism

Measurement of bone metabolism markers has been demonstrated to correlate with current bone density, rate of bone loss, and fracture risk [29]. However, the correlations are not strong enough to predict bone mass or fracture risk for a given individual. Hence, the clinical usefulness of biochemical markers is limited, but they are widely used for research purposes [25]. Many of the bone turnover markers have a circadian rhythm with peak concentration in the morning and nadir in the mid to late afternoon. Sampling should therefore be standardized to a given time interval. In this thesis, osteocalcin and β -CTx have been used. These and other frequently

used markers are briefly described below.

Bone formation

Osteocalcin

Osteocalcin (OC), also referred to as bone γ -carboxyglutamate protein, is a small non-collagenous calcium- and hydroxyapatite-binding protein (5.8 kDa) that is specific for bone tissue and dentine [30, 31]. The protein is synthesized by osteoblasts and the formation is dependent on vitamin K and stimulated by 25-OH-vitamin D. A fraction of the protein is released into the circulation where it can be measured. OC also acts as a hormone by stimulating β -cell proliferation in the pancreas and insulin secretion, and also by acting on the adipocytes to induce adiponectin that reduces insulin resistance, thereby interacting

with glucose and fat metabolism [21-23]. The plasma elimination of osteocalcin is mainly dependent on kidney function [32]. Temporary changes in osteocalcin levels have been demonstrated in young women and early postmenopausal women following physical exercise [33, 34]. The level of OC is negatively correlated with total body BMC [35]. Since OC is cleared by the kidneys, serum concentrations can be elevated in patients with renal failure. OC is widely considered the best marker of bone turnover and formation and may be useful for predicting fractures [36, 37].

Bone-specific alkaline phosphatase

Alkaline phosphatases are plasma membrane enzymes that are produced by many tissues. Most of the circulating alkaline

phosphatase originates in bone and liver. Bone-specific alkaline phosphatase (BSAP) is produced by osteoblasts and correlates with bone mineralization rates. Assays with antibodies specific for BSAP have been developed, and the precision and specificity are acceptable, although some cross-reaction with the liver form. As alkaline phosphatase is cleared by the liver, it may be elevated in patients with liver disease. [24].

Procollagen 1 extension peptides

Type I collagen is synthesized by the osteoblast as a procollagen precursor molecule. The C- and N-terminal ends are cleaved enzymatically before the collagen becomes incorporated in the bone matrix. The cleaved peptides, carboxyterminal propeptide of type I collagen (P1CP) and

aminoterminal propeptide of type I collagen (P1NP), can be measured as markers of bone formation, but are not as useful as BSAP or OC [24, 25]. Because type I collagen is not unique to bone, the peptides are also produced by other tissues that synthesize type I collagen [25].

Bone resorption

C-telopeptide of collagen cross-links

During normal bone metabolism, mature type I collagen is degraded and small fragments pass into the bloodstream and are excreted via the kidneys. In physiologically or pathologically elevated bone resorption (e.g. in old age or as a result of osteoporosis), type I collagen is degraded to an increased extent, and there is a commensurate rise in the level of collagen fragments in blood.

Especially relevant collagen type I fragments include the C-terminal telopeptides (CTX). In the C-terminal telopeptides, α -aspartic acid present converts to the α -form of aspartic acid as the bone ages (α -CTX) [38, 39]. The α -CTX is specific for the degradation of type I collagen dominant in bone, and elevated serum concentrations have been reported for patients with increased bone resorption [40, 41]. There are also assays available to detect α -CTX in the urine. By determining this bone resorption marker, the activity of bone turnover and vertebral fracture risk can be estimated [24, 37]. α -CTX may also be used as a sensitive marker for detecting changes during treatment [24].

N-telopeptide of collagen cross-links (NTx)

NTx is the N-terminal degradation product of type I collagen. Assays to detect NTx in both serum and urine are available. NTx is also shown to be a sensitive marker in detecting changes during treatment [24].

Collagen pyridinium crosslinks

In type I collagen there are two major crosslink molecules, namely pyridinoline (PYD) and deoxypyridinoline (DPD). These molecules are released from bone only during bone resorption and collagen breakdown. DPD has greater specificity because PYD is present to some extent in type II

collagen of cartilage and other connective tissue [25]. The excretion of these molecules in the urine reflects the degradation of mature collagen and may be used for monitoring bone resorption [24].

Acid phosphatase

Acid phosphatases are a family of lysosomal enzymes that are present in many cells. Osteoclasts contain the isoenzyme tartrate-resistant acid phosphatase 5b (TRACP5b), which is present in large quantities in the ruffled border of osteoclasts and which is released during bone resorption [24]. The TRACP5b may be used for the prediction of vertebral fractures [37].

Bone measurements

There are several techniques for measuring bone mass. Below is a brief description of methods currently available.

Dual energy X-ray Absorptiometry

The 'gold standard' for measurement of BMD and BMC in both research and clinical practice application is the dual energy X-ray absorptiometry (DXA) measurement. DXA technology uses very low dose X-rays at two different levels to distinguish between bone, lean body mass (g) (mainly consisting of muscles and blood), and fat mass (g). The radiation exposure for a patient during a whole body composition scan corresponds to approximately one day of natural background radiation, which is

1,000 times less than the limit for trivial exposure, and it is classified as a negligible individual dose.

The exposure during a bone density scan at the lumbar spine or the hips is slightly higher than during a body composition scan.

The effective doses of radiation exposure to the body during DXA measurement lie at 1–5 μSv [42]. Natural background radiation in Sweden is estimated at 4 mSv per year [43].

DXA scans are most often performed on the lumbar spine and hips. Subject should wear loose, comfortable clothing, avoiding garments with zippers, belts or buttons made of metal. In order to assess the spine, the patient's legs are supported by a padded box in order to flatten the pelvis and lumbar spine. To assess the hip, the patient's foot is placed

in a brace that rotates the hip inward. In both cases, the detector slowly passes over the area, generating images on a computer

monitor. Each DXA bone density scan is usually completed within five minutes



Fig. 2. DXA equipment.

The current generation of DXA can also provide lateral images of the spine for Vertebral Fracture Assessment (VFA). This method can be used to detect vertebral fractures by using the semi-

quantitative system of Genant for grading of vertebral deformities [44, 45]. VFA cannot be used to detect other vertebral abnormalities.

Despite its effectiveness as a method of measuring bone density, DXA is of limited use in people with a spinal deformity or in those who have undergone previous spinal surgery. The presence of vertebral compression fractures or osteoarthritis may interfere with the accuracy of the test and may falsely indicate high BMD. Furthermore, bone size affects the measurement as DXA measures aBMD expressed in g/cm^2 , and not true volumetric bone mineral density (vBMD, g/cm^3). This discrepancy makes larger bones appear denser. Extreme obesity may also

interfere with the measurement and falsely indicate low BMD values. The precision error for a DXA measurement is 1–2% for lumbar spine and 1.5–3% for the hip [42].

T-scores and Z-scores are derived from the BMD measurement at the lumbar spine and hips, and these values are used for the diagnosis of osteoporosis. The DXA scan is currently the only method that can be used to diagnose osteoporosis, as no reference data are available for the management of the diagnosis for the other methods.

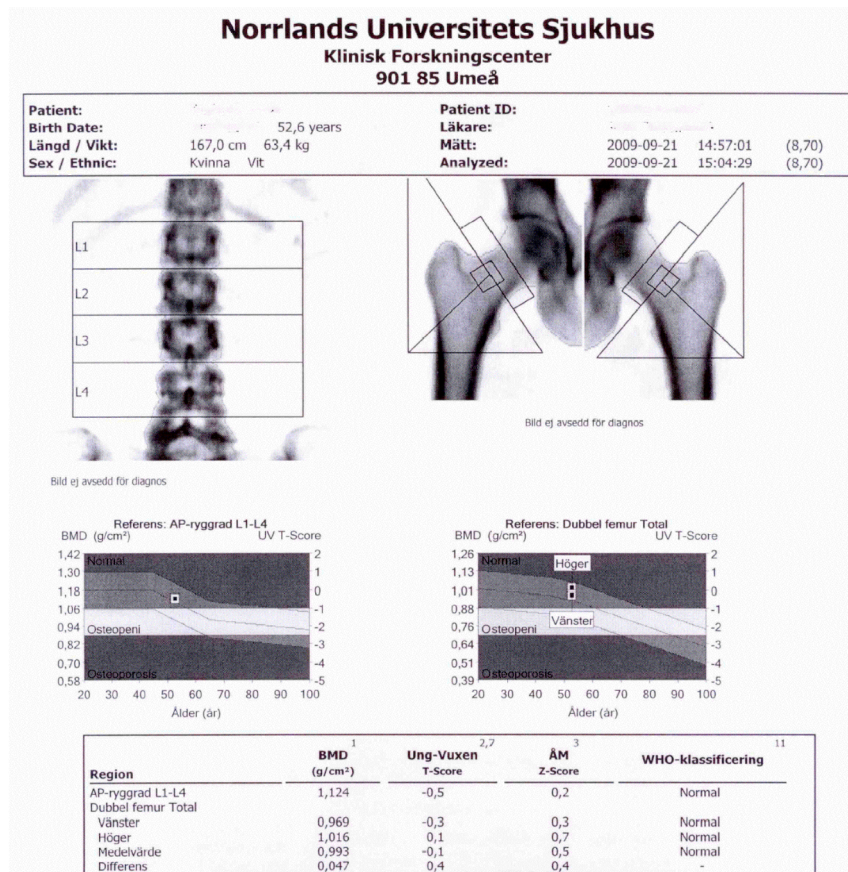


Fig. 3. Report from a DXA-measurement of the femoral neck and lumbar spine.

Peripheral DXA

Peripheral DXA (pDXA) equipment for the measurement of forearm, fingers, and calcaneus is also available. This type of equipment has the advantage of being inexpensive, small, and

portable. The WHO diagnostic classification can be applied to the one-third-radius region measured by pDXA [43, 45]. The precision error for pDXA is 1–2% [42], and validated pDXA devices can be used for predicting vertebral and global fragility fracture risk in

postmenopausal women. However, as yet the same prediction for men is not possible due to a lack of evidence [45].

Single X-ray absorptiometry

Single X-ray absorptiometry (SXA) is a measurement method that is not used as frequently these days. This measurement method requires a water-bath surrounding the region of skeleton to be measured. The method can be used for measuring BMD in distal forearm and calcaneus. The precision error for SXA is 1–2% [42].

Quantitative computerized tomography

A central quantitative computerized tomography (QCT) measures lumbar spine BMD. QCT differentiates cancellous from cortical bone and measures

true volumetric BMD (vBMD) in g/cm³. The size of the vertebrae does therefore not influence the result. BMD measured by QCT has the same ability to predict vertebral fractures as BMD measured with central DXA in postmenopausal women, but there is a lack of evidence for men and also for hip fracture prediction in men as well as in women. QCT can be used to monitor age-, disease-, and treatment-related BMD changes. The dose of radiation is higher than for DXA measurements and the precision error is 1.5–4% for QCT [42, 45].

Peripheral quantitative computerized tomography

A peripheral quantitative computerized tomography (pQCT) can be used for measuring vBMD of the forearm or tibia. A

pQCT can be useful for measuring bone density in children. pQCT of the forearm at the ultra distal radius predicts hip, but not spine, fragility fractures in women [45]. For men there is a lack of evidence relating to this measurement method. The radiation dose for pQCT is lower than for the central QCT and the precision error is 1–2% [42, 45].

Quantitative ultrasound

Quantitative ultrasound (QUS) equipment is inexpensive, does not cause ionizing radiation exposure, and is portable. The only validated skeletal site for clinical use is the heel, although devices have been developed to probe the radius, tibia, and finger phalanges. The validated QUS can be used to predict fragility fracture risk in postmenopausal women (hip, vertebral, and global

fracture risk) and men over the age of 65 years (hip and all non-vertebral fractures). However QUS cannot be used for monitoring skeletal effects of osteoporosis treatment and is not recommended for clinical usage [46]. The QUS measures speed of sound (SOS) expressed in m/s, or broadband ultrasound attenuation (BUA) expressed in dB/MHz, not BMD. Stiffness index and quantitative ultrasound index may be estimated from a mathematical combination of SOS and BUA. The estimated parameters are lower for osteoporotic patients than for non-osteoporotic individuals. The precision error for BUA is 2–3.5% [45-47].

Lifetime changes in bone mass

During childhood and adolescence, rapid linear and appositional bone growth occurs. Peak bone mass (PBM), when the skeleton contains its greatest mass of bone, is reached in the third decade of life [48]. The bone mass acquired at the end of the growth period appears to be of importance for the future risk of osteoporosis. PBM is greater in men than in women when expressed as aBMD, which corrects only partly for bone size. There are also interracial differences, with higher values among American blacks than in Caucasians.

The rate of bone loss varies among the skeletal sites, with greater losses of cancellous bone than cortical bone due to a higher

remodelling rate in cancellous bone. Cortical bone loss begins in middle life whereas cancellous bone loss starts already in young adults. Young women lose about 1.6% per year at lumbar spine before the age of 50 years, and the corresponding figure for young men is 0.8 % per year. Women experience accelerated bone loss for about five to eight years after menopause, during which period they can lose nearly 3% per year at the lumbar spine. After the accelerated menopausal bone loss, women continue to lose about 0.2–0.6% at distal radius and distal tibia, and 2.6% at the lumbar spine annually. For men over the age of 50 years, the losses are 0.2–0.4% annually at distal tibia and radius and 1.8 % at the lumbar spine [49]. The accelerated menopausal bone loss in women is associated with both

high bone turnover and remodelling imbalance with a higher rate of resorption than formation [50, 51]. The remodelling imbalance is caused by an uncoupling of the phases of bone remodelling, with a relative or absolute increase of the resorption over bone formation, resulting in a net loss of bone. Oestrogen acts directly on the osteoblasts to increase bone formation and to increase osteoblastic formation of OPG, which in turn inhibits bone resorption [52]. Menopausal bone loss appears to be a direct consequence of oestrogen deficiency [51, 53].

Longitudinal bone growth ceases after puberty whereas net periosteal apposition continues throughout life, so the width of several bones increases with age. The process of endosteal bone resorption takes place simultaneously, and as a result of the remodelling imbalance the width of cortex decreases with age. The cortical bone also becomes more porous with age, which has been referred to as ‘trabecularization’ of cortical bone. Further, there is an accumulation of microdamages in the cortices, which increases the fragility of the bone [51].

Osteoporosis

The term ‘osteoporosis’ means ‘porous bone’ and was first introduced in France and Germany in the 19th century. It

initially implied histological diagnosis, but was later refined to mean bone that was normally mineralized, but reduced in quantity [24].

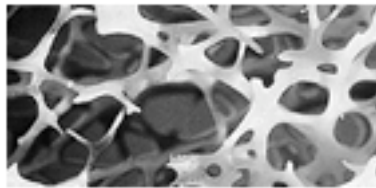


Fig. 4. Healthy bone

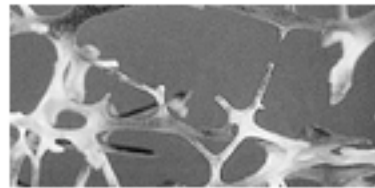


Fig. 5. Porous bone

The World Health Organization (WHO) did not define osteoporosis until 1993 and explains it as ‘a systemic skeletal disease, characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures’ [54]. Osteoporosis is diagnosed by measuring bone

mineral content (BMC) or bone mineral density (BMD) at the lumbar spine or hips using whole body DXA (see p27). BMC is expressed in gram, but BMD is also referred to as areal BMD (aBMD), which is BMC/area and consequently expressed in g/cm².

Diagnostic criteria

Diagnostic thresholds are defined for postmenopausal women, but not for men, based on the distribution of BMD in the young female population and is

expressed in terms of standard deviation units (SD) or a T-score which is equivalent to SD [16, 45, 55, 56]. This permits four general diagnostic categories for postmenopausal women (Fig. 6).

Normal	BMD or BMC value not below 1 SD below the average value of young females
Osteopenia (low bone mass)	BMD or BMC value of 1–2.5 SD below the young normal average
Osteoporosis	BMD or BMC value 2.5 SD or more, below the young average
Established osteoporosis	Osteoporosis and the presence of one or more fragility fractures

Fig. 6. WHO's diagnostic thresholds.

The distribution of BMD values is Gaussian in all ages but decreases progressively with age. Hence, the proportion of women with T-score ≤ -2.5 increases exponentially with age. Diagnostic criteria are not

defined for men, but normally the same thresholds can be used for men aged 50 or older, along with a young male reference population. For premenopausal women and men younger than 50

years, a Z-score should be used instead [45, 57]. A Z-score is defined as the number of SD above or below the mean for the patient's age and sex.

Low bone density itself causes no symptoms and progressive bone

loss is therefore sometimes referred to as the 'silent epidemic' or 'silent thief'. Related morbidity is caused by painful fractures.

Fractures

The definition of an osteoporotic or fragility fracture is a fracture following low trauma, such as a fall from standing height or less. The most common fragility fractures are wrist, vertebral, and hip fractures, which are described more thoroughly below, but humeral and pelvic fractures are also most often osteoporosis related.

Wrist fracture

The wrist fracture, also referred to as distal forearm fracture, is the most common fragility fracture with an incidence of 25,000/year in the Swedish population [58]; the mean age for this type of fracture is around 64.0 years [59]. The lifetime risk for a 50-year-old Swedish woman to suffer a wrist fracture is 21%, whereas the same risk for a 50-year-old man is 5%

[16]. The global burden of wrist fractures was estimated at 1.7 million fractures in the year 2000 [60]. A wrist fracture usually occurs when a falling person extends an arm to break the fall. The hand and forearm absorbs all the weight and force resulting from the fall, and the wrist breaks as a consequence. In some studies, physical activity, especially brisk walking, has been proposed as being a risk factor for this type of fracture [61-64], but some studies have also found that physical activity protects against wrist fractures [65]. Most often the broken wrist can be treated with closed reduction and a cast, but some wrist fractures require surgery. The mean loss of quality of life is estimated to be lower than for hip fractures [66], and no increased mortality has been

observed following wrist fractures.



Fig. 7. Wrist fracture

Vertebral compression fracture

Approximately 15,000 vertebral compression fractures receive clinical attention in Sweden annually [58]. However, the total number of actual vertebral compression fractures is probably three times higher than this

estimate as about two thirds of people with vertebral fractures do not seek medical attention. The lifetime risk for a 50-year-old woman in Sweden of sustaining a vertebral compression fracture is 15%, and for a 50-year-old man the same risk is 8% [16]. The age-adjusted risk of mortality in the

first year following a fracture is elevated 9–10-fold [12, 13]. The quality of life is severely reduced after a vertebral compression fracture, and the risk of getting a new vertebral fracture during the first year is 19.2% [46]. The major risk factors for suffering a vertebral compression fracture are a previous fracture and low BMD. The fracture may occur as a

consequence of minimal trauma such as picking up a bag of groceries, picking something up from the floor, or jarring the spine by missing a step. In people with very advanced osteoporosis, the fracture can even occur with extremely minor activity, such as sneezing, coughing, or simply turning over in bed.

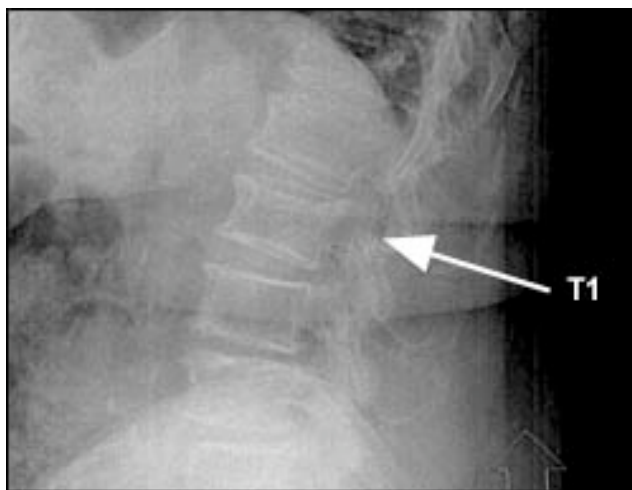


Fig. 8. Vertebral compression fracture.

Hip fracture

Hip fractures are the most serious complications of osteoporosis and they cause great suffering, reduced quality of life for survivors [67], and high associated costs for society [17]. A hip fracture occurs most often when a person falls on the greater trochanter instead of parrying the fall with an extended arm, and most hip fractures occur indoors in the person's home. All hip fracture cases are admitted to hospital and require surgical treatment. The hip fracture is associated with both high morbidity and high mortality. Thus, only 50% of these patients reach the same functional level that they were at prior to trauma [68]. The age-adjusted risk of mortality in the first year

following a fracture is elevated 7–9-fold. This elevation is partly explained by comorbidity resulting from the fact that hip fracture patients more frequently suffer from other diseases compared to the general population [12, 13, 16]. In Sweden, the age-adjusted incidence of hip fracture is about 390/100,000 men and 779/100,000 women [5], and the mean age for hip fracture patients in Sweden is around 81 years [9]. Women are at about twice as high a risk for suffering a hip fracture than men, and the probability for a 50 year old Swedish woman to sustain a hip fracture at some point of her remaining life is about 23% whereas the same risk for a man is 11% [16]. One risk factor for hip fractures is body height, i.e. tall women are at

about twice as high a risk of a fracture than short women, due to the hip axis being longer in taller individuals which causes a higher

transmission of impact energy to the femoral neck at the time of a fall on the hip [69-72].



Fig .9. Hip fracture.

Risk factors for osteoporosis and fragility fractures

The aetiology of osteoporosis is multifactorial; inadequate peak bone mass, bone loss due to increased age, and gonadal insufficiency are the major determinants [54]. However, a number of other risk factors aside from age and hormonal causes have been identified and suggested to be associated with the outcome of osteoporosis. These risk factors include genetic factors, and lifestyle, including dietary habits, physical inactivity, medical conditions, smoking habits, and alcohol and drug use [73, 74]. Medical conditions include a variety of endocrine diseases such as gonadal insufficiency, primary hyperparathyroidism, thyrotoxicosis, diabetes mellitus,

and Cushing's syndrome, as well as inflammatory bowel diseases, rheumatoid arthritis, and chronic obstructive pulmonary disease [75]. Nutritional habits include insufficient intake of calcium and vitamin D. Low exposure to sunlight also contributes to low vitamin D levels. The most common and well-known medication group that increases the risk for osteoporosis is corticosteroids [19, 24].

Although bone density is an important determinant of future fracture risk, other factors may also, independently, increase the risk of fractures. These include factors that increase the risk of falling, e.g. impaired vision, muscle weakness, impaired balance and gait, and the use of certain drugs such as antidepressants and neuroleptics

[73, 76]. Medical conditions such as depression and dementia are also associated with increased fall risk [77-79]. Furthermore, a previous fragility fracture has been shown to be an independent and strong risk factor for a new fracture [76, 80, 81].

Recently, the new fracture risk assessment tool FRAX™ has been developed and may prove useful especially in primary care. By combining well-established risk factors for fracture both with and without BMD, the risk for an osteoporotic fracture in the next ten years can be estimated. The

clinical risk factors used in this model include BMI, a prior history of fragility fracture, a parental history of hip fracture, use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current smoking, and alcohol intake of three or more units a day [82]. Fracture probability varies around the world, so the model is calibrated with country-specific epidemiological characteristics in mind. A specific model has been developed for Sweden. The model is computerized and freely available on the Internet (www.shef.ac.uk/FRAX).

Physical activity

The influence on bone mass

Bone is an adaptive tissue which develops in structure and function in response to the mechanical loading applied to it [83, 84]. Thus, skeletal modelling and remodelling are directly related to the functional requirements of the tissue. All forces applied to bone produce deformation or strain in the bone [84, 85]. An optimal level of strain is necessary to maintain bone mass [86]. Experimental studies on rats have demonstrated that a loading regimen should be dynamic rather than static, produce high strains in unusual patterns during short periods and should be repeated regularly to evoke the greatest osteogenic response [84]. In a cross-sectional study by Nordström P [87], badminton

players had higher BMD in the trochanter and distal femur compared to ice-hockey players and controls. Those findings could be an expression of the association between loading regimen and BMD, since badminton players perform jumping in unusual directions. Several other studies have also suggested that activities that encompass high weight-bearing loading seem to be more effective than non-weight-bearing activities such as swimming and bicycling [88-90]. The osteogenic effect of mechanical loading is site-specific. Thus, higher bone mass has been found in those skeletal sites that are stressed by the particular loading regimen [91].

It is well known that physical activity is beneficial for bone health in both children and

younger men and women, especially if the activity started before or during puberty [92, 93]. Cross-sectional studies generally show about 10% higher bone mass in athletes compared to age matched controls [94-98].

Even though exercise is beneficial for bone health in adolescence and young adulthood it still remains unclear whether the exercise induced bone gain is preserved into adulthood and whether it can prevent future fractures. Longitudinal studies on young athletes implicate that bone density rapidly decreases to pretraining levels after they have ceased from their activity [99, 100]. Although male athletes who retired from sports lost more BMD than controls and still active athletes, former male athletes

aged 60 years and above had fewer fractures than controls [99].

Several intervention studies have been performed on premenopausal and younger postmenopausal women and have suggested that exercise or physical activity can preserve or even increase bone mass at the lumbar spine and proximal femur [98, 101-105]. There are only a few randomised studies on women with a mean age above 70 years. One study [106] examined the effect of weight-lifting training, and another study [107] investigated the effect of a weight-bearing programme including strengthening, coordination, and balance exercises. Those studies did show significant improvements in muscle strength but not in bone mineral density. Studies with older

postmenopausal women performing jumping exercises have not shown any effects on bone mass [108-110]. One study even indicates that intensive high impact exercise, such as jumping, may cause a reduction in regional bone mass [109]. Walking is an activity that may be suitable for many older women, but in the meta-analysis of eight eligible trials walking showed no benefits of BMD in the lumbar spine, whilst it had some effects on the femoral neck [111]. Other studies on older women have shown benefits on bone density and neuromuscular function induced by exercise [106-108, 112-114]. Very few studies have investigated the effect of detraining on bone density in older individuals. The few detraining studies that have been performed in postmenopausal women suggest

that bone density rapidly decreases to pretraining levels after a physical intervention has stopped [115, 116], whereas detraining studies in premenopausal women have yielded mixed results [117, 118].

The relationship between muscle strength and BMD is also an important research topic mainly because both muscle strength and BMD decline with age and age-related decline in muscle strength has been proposed to be attributable to an age-related bone loss [119, 120]. Cross-sectional studies have investigated the relationship between muscle strength and BMD of adjacent bone, and many of them have demonstrated a site-specific relationship [98, 101, 121-123]. It has therefore been suggested that muscle-strengthening exercises

potentially also increase BMD [124].

The influence of physical activity on neuromuscular function, falls, and fracture risk

Falls are common in older people, and may lead to disability and loss of independence [125, 126]. There is a normal decline in neuromuscular function with age, which has been suggested to increase the risk for fractures since most of the fractures are preceded by a fall [127, 128]. Neuromuscular impairment such as reduced gait speed is a significant and independent predictor of the risk of hip fracture in elderly mobile women [129], and earlier studies suggest that physical activity significantly reduces the risk of falls and fractures by improving muscle strength and balance [107, 130,

131]. Physical training has the propensity to increase neuromuscular functions such as balance and gait besides muscle strength, and thus may protect against falls and fractures. Further, there is evidence that physical training in old age decreases the risk of falling [132, 133]. Women who are moderately physically active have shown a reduction in their risk for hip fracture compared to sedentary controls [134]. Other studies have confirmed an inverse relationship between physical activity and the risk of hip fracture in men [135, 136], and in both men and women [137, 138]. A recent meta-analysis of 13 prospective cohort studies performed by Moayyeri, confirmed that moderate to vigorous physical activity was associated with a reduction in hip

fracture risk in women as well as in men [139].

In general, physical activity seems to be beneficial for bone density, muscle strength, balance and perhaps also fracture risk, but for wrist fractures most studies have shown increased risk for women with a high level of physical activity [63, 64], and especially for brisk walking [61], implicating that wrist fracture mostly occurs among women who are relatively healthy and active.

Some studies have been performed on the effects of detraining on neuromuscular function in older subjects, but the results are varied. One randomised controlled trial in older women (75–85 years) showed sustained benefits pertaining to the risk of falling for at least 12 months after a

resistance-training programme had ceased [140], whereas another study showed decreases below baseline level in quadriceps strength and walking speed in older women (mean age 83 years) one year after a strength-training programme had stopped [141]. It may be possible to maintain some of the benefits relating to physical functioning after an exercise programme has finished, but at a minimum some moderate activity must continue [142]. One study compared the effects of detraining in younger and older subjects and found that older subjects (> 65 years) had a significantly higher decline in exercise-induced muscle strength than younger subjects [143], suggesting that the negative outcome of cessation of training is affected by age.

Gregg and co-writers [144] demonstrated a significant reduction in the age-adjusted risk of hip fracture among physically active women compared with inactive women and recommended low-intensity physical activity for sedentary older women as a form of fracture prevention. A study by Nguyen TV et.al. on men exclusively showed no fracture risk reduction with physical activity when adjusted for BMD [145]. Prospective

studies evaluating whether lifelong exercise protects against fragility fractures are difficult to carry out and to date no such studies with fractures as end point have been performed. Studies on the effects of occupational, sports, and leisure activities on bone mass, neuromuscular function, and fracture risk in middle age, have showed inconsistent results.

Vitamin D, balance, muscle strength, and fracture risk

Vitamin D is involved in bone metabolism through stimulation of calcium absorption from the intestine and resorption from the kidneys. It also has direct effects on the osteoblasts and osteoclasts as well as indirect effects through PTH [24, 146]. There are also potential effects not only on bone but on balance and neuromuscular functions [147-153]. Expression of highly specific vitamin D receptors has been demonstrated in myoblast cell lines [154] in human skeletal muscle [155], as well as in osteoblasts [156]. It is proposed that the binding of $1,25(\text{OH})_2\text{D}$ to these receptors promotes protein synthesis and affects cellular growth. Low vitamin D levels are

also associated with secondary hyperparathyroidism, increased bone remodelling, and subsequent bone loss [157]. Thus, vitamin D deficiency predisposes to fracture by two independent pathways: increased likelihood of falling and increased bone fragility. Vitamin D is synthesized in the skin in the presence of ultraviolet B light (UVB 290–315 nm). In northern regions there is insufficient sun light exposure during the winter season for the synthesis of vitamin D in the skin, and in the elderly the capacity of the skin to synthesize vitamin D is also reduced which results in lower vitamin D levels with aging. In a recent study in Umeå in northern Sweden, plasma levels of $25(\text{OH})\text{D}$ below 50 nmol/l was a strong and independent risk factor for hip fracture in subjects over 60 years [158].

Rationale for the thesis

The problems associated with osteoporosis and fragility fractures are common and on the rise globally. Along with the increasing number of elderly, the so-called age quake, we can expect these problems to increase further with great suffering for affected individuals and high costs for society as a result. Nowadays, many people lead a sedentary lifestyle, and occupational activity is not generally as hard as it was in the past. Weight-bearing physical activity is known to be

beneficial for bone density, and if physical activity as such can alter the course of the disease before it has even developed, or at least prevent falls and fractures from occurring, it may be the easiest and most cost-effective prevention/treatment available. However, there is currently a lack of studies that investigate the true effect of physical activity on bone health and fracture risk in older women. The few studies available show inconsistent results, and as a consequence this is an area that would benefit greatly from further research.

Aims and hypotheses of the thesis

The aim of this thesis was to study the association between physical activity, bone mass, and fractures in older women. The main hypothesis was that physical activity has the propensity to increase or preserve bone density, be beneficial for muscle strength and balance, and prevent future fractures even in old age. The specific aims were as follows:

Study I – investigate whether a combined weight-bearing training programme was suitable for older community living women in general, and to determine the effects of the programme on bone mineral density, muscle strength, gait, and balance.

Study II – investigate whether any of the positive effects on bone density and neuromuscular function following a 12-month combined weight-bearing programme were maintained in older women, five years after cessation of training.

Study III – investigate whether commuting, occupational, and leisure activities were associated with a decreased risk of later sustaining a hip fracture in middle-aged women.

Study IV – investigate whether a physically active lifestyle in middle age was associated with the risk of later sustaining a wrist fracture in women.

Materials and methods

Study I and II

Subjects

Study I and II are based on a cohort of female volunteers recruited from the University for the Elderly in Umeå, Sweden and a group of women born 1920 that had already participated in a previous study called U-70. Forty-eight volunteers were eligible for randomisation. The mean age was 73 years (range 66 – 87) and none of them were institutionalised. They were pair-wise age-matched and randomised to either an intervention group or a control group. Of the randomised subjects, 40 (21 in the intervention group, 19 in the control group) completed the whole study-year (study I). Dropouts from the intervention

group occurred due to dementia (n = 1), heart failure (n = 1), and knee pain (n = 1). Dropouts from the control groups occurred due to lack of interest (n = 2), training on a regular basis (n = 2), and death (n = 1). Of those who completed study I, 34 (18 from the intervention group, 16 from the control group) were able to take part in the follow-up study five years later (study II). The dropouts that occurred during the five years between study I and II were due to death (n = 2) and dementia (n = 1) in the intervention group. In the control group the reasons for dropout were death (n = 1), dementia (n = 1), and unknown reason (n = 1). During the five years in between, some subjects attended voluntary exercise training classes independently of which group

they belonged to in study I. (Fig
10)

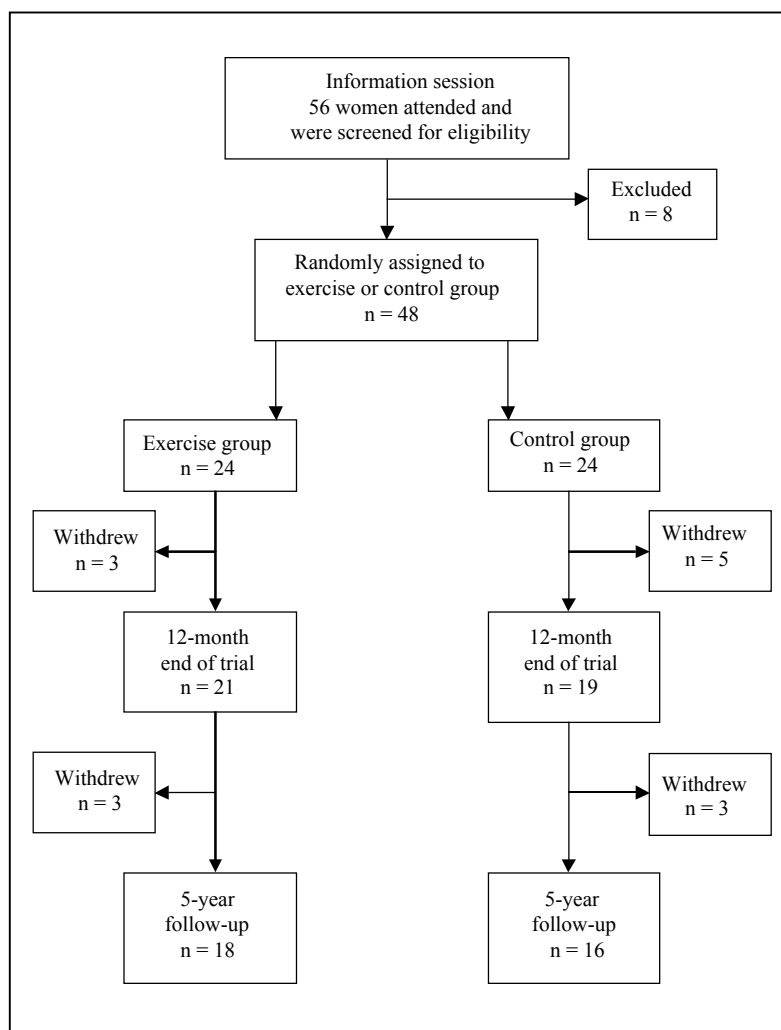


Fig . 10. Flow chart of subjects in study I and II.

Assessments

All BMD and BMC measurements in study I and II were performed on the same DXA machine, a Lunar DPX-L, software version 1.3y (Lunar Co., Wis., USA). In order to minimize inter-observer variation, the same technician made all the measurements. The coefficient of variation (CV-value) (standard deviation/mean) for repeated measurements was estimated at 0.7% (total body), 2.2% (head), and 1.0% (arms). CV-values for the femur and spine software were 0.8% (neck), 1.2% (Ward's), 1.5% (trochanter), and 0.6% (lumbar spine), respectively. CV-values for body fat percentage, fat mass, and lean body mass were 3.9%, 2.6%, and 0.9%, respectively.

Two physiotherapists performed the assessments of physical activity, in addition to the exercise programme, by using the Frändin-Grimby activity scale [159] and the neuromuscular function tests of isometric grip strength, isometric quadriceps strength, maximum walking speed, and balance. Medical examination of the subjects was performed by two physicians. Blood tests were taken as part of a general health check in both studies. Both the physiotherapists and the physicians performed cross-examinations to ensure inter-observer reliability. Due to a lack of resources none of the investigators were blinded to which group the subject belonged.

In study I, the dietary intake of vitamin D ($\mu\text{g/day}$), calcium (mg/day), and energy (kcal/day)

were assessed at baseline and follow up. Food composition was calculated with MATS software (MATS program, version 4.0., Västerås, Sweden: Rudans Lättdata 1997).

In study II, all participants were also asked to donate a blood sample for analysis of serum vitamin D metabolites and markers of bone metabolism. The markers analysed were β -CTx and osteocalcin in serum. All blood samples were donated at the beginning of the month of June, and the blood was drawn in the morning and the resultant serum was kept frozen at -70°C until assayed.

Intervention

In study I, the intervention group performed an exercise programme supervised by a

physiotherapist for 50 minutes twice a week for twelve months. The programme was carried out to music and was supervised by a physiotherapist. The programme begun with a 10 min warm-up, followed by a mix of aerobic, strengthening, balance, and coordination exercises, lasting for 27 min. The programme ended with 11 min of cooling down, stretching, and relaxation. The programme was designed to load bones with intermittent compressive forces, introducing stress to the bone, which is known to improve skeletal integrity [84] and neuromuscular functions. The intensity of the programme was self-paced and the subjects were allowed to rest if necessary. If a participant missed a training session she was advised to perform a home exercise programme instead. The women

in the control group were asked not to increase their normal physical activity during the study year.

Study III and IV

Subjects

The subjects in study III and IV were women from the Västerbotten Intervention Program (VIP) cohort. Since 1985 all inhabitants aged 40, 50, and 60 years old in the county of Västerbotten have been invited to take part in a health survey every ten years, and have been asked to donate blood for research purposes and to answer an extensive self-administrated questionnaire concerning their general health, education, occupation/work, and lifestyle. Fracture cases were identified from a prospective injury-fracture database at the Umeå University

hospital and merged with the VIP database to identify those who had filled in a questionnaire before they sustained a hip or wrist fracture. These were compared with 1-2 controls selected from the same database and matched for age at recruitment and date of answering the questionnaire. In the hip fracture study (study III) the total cohort consisted of 237 subjects, and the wrist fracture study (study IV) contained a total of 778 women.

Assessments

All subjects had filled in an extensive self-administrated questionnaire about their general health, menopausal status, education, occupation/work, and lifestyle such as physical activity, smoking habits, alcohol habits, and use of medications and

supplements. The questionnaire had been filled in prior to when the cases sustained their fractures. The questions concerning physical activity included those below. Commuting activities defined in three categories: travelling by car or bus (0 points), bicycling (1 point), and walking (2 points). The commuting values for each of the four seasons were then added up, resulting in a maximum of 8 points for each subject. The subjects were thereafter divided into three 'commuting activity' groups: low (0–2 points), moderate (3–5 points), and high (6–8 points). Occupational physical activity was divided into three groups: low, moderate, and highly physically demanding work. Exercise in training clothes during the last three months was divided into two groups:

performed and not performed, Physical activity in youth was defined as three groups: physical training at school only, training and/or competing at amateur level, and competing at elite level. Questions relating to leisure activities were based on seven different regular activities (walking, bicycling, dancing, snow shoveling, gardening, hunting/fishing, and berry/mushroom picking). Walking or bicycling at least 2–3 times/week yielded 1 point each. The remaining activities yielded 1 point each if performed at least once a month, resulting in a maximum of 7 points for each subject. In study III, the subjects were then divided into three leisure activity groups: low, moderate, and high, defined as 1–2 points, 3–4 points and 5–7 points, respectively. In study IV,

the leisure activities were coded as: walking and bicycling 1-2 times/month or less (=low), 3-4 times/month (=moderate), and 2-3 times/week or more (=high), and the remaining activities (dancing, snow shoveling, gardening, hunting/fishing, and berry/mushroom picking) were coded as not performed (=0) or performed (=1) if performed at least every month.

Statistics

Study I

All data were analysed with the SPSS package, versions 6.0 and 11.0 (SPSS Inc., Chicago, USA) for Macintosh. Student's *t*-test for independent samples was used to test for differences between the control group and the exercise group. In order to correct for different baseline values when

analyzing the inter-group significance of changes, we also performed analysis of covariance (ANCOVA) by using baseline values as the covariate [160]. Changes from baseline and over the 12-month training period were evaluated with paired *t*-tests. Multiple regression models were adapted to analyze the effect of the training activity in the presence of other predictor variables. Possible interaction was examined between training activity, age, weight, BMI, age at menopause, weight loss before the study, and baseline values. Bivariate correlations were also measured in the respective groups between the changes in outcome variables and different explanatory factors; Pearson's coefficient of correlation was used for this purpose. Results were considered significant at a P-level

below 0.05. Power calculations were performed for BMD, muscle strength, and maximal walking speed. A sample size of 24 subjects in each group, an α -level of 0.05, and a standard deviation of 10% gave 30% power to detect a 5% difference in change between the two groups as well as intra-group differences.

Study II

The SPSS package, version 11.0 (SPSS Inc., Chicago, USA) for Macintosh, was used for data analysis. Student's *t*-test for independent samples was used for comparing differences between the two groups over the 5-year follow-up period and from baseline to follow-up. Intra-group changes over the 5-year follow-up period were evaluated using paired *t*-tests. In order to correct for different end-of trial values

when analysing the inter-group significance of changes, we also performed ANCOVA using end-of-trial values as the covariate [160]. Stepwise multiple regression analyses were used to identify predictors of changes in BMD and BMC between the end of the trial and the follow-up visit. Years since menopause, body weight, height, lean mass, fat mass measured at the follow-up visit as well as the percentage of change in height, body weight, and neuromuscular parameters were entered into the model. Results were considered significant at the level of *P* below 0.05.

Study III and IV

Tests for baseline differences were carried out using STATA™, version 8 (Stata Corporation, Texas, USA) for Macintosh, and statistical analyses using

conditional logistic regression were carried out using R version 2.9.0 (www.r-project.org). Baseline differences between the groups relating to physical characteristics and prevalence of risk factors were determined by using Student's t-test and chi-square tests. A P-value of less than 0.05 was considered significant. To investigate if the candidate risk factors were independent risk factors, confounders or effect modifiers, Spearman's correlation was used. Odds ratios (OR), as an estimate

of the relative risk for fracture, were calculated for matched sets of cases and controls using at first univariate conditional logistic regression separately for the different physical activities, followed by multiple conditional logistic regression with the physical activities selected from the univariate regression analyses, and adjusted for height, BMI, smoking habits and menopausal status. Subanalyses with alcohol habits and hormon replacement therapy (HRT) were also made.

the Medical Faculty, Umeå University, approved the studies.

Ethics

All subjects gave their informed consent. The Ethics Committee of

Summary of results

Study I

A 1-year combined weight-bearing training programme is beneficial for bone mineral density and neuromuscular function in older women

The only significant differences between the groups at the beginning of the study were BMD at the Ward's triangle and the mean age for menopause. There were no significant changes in either group in the level of physical activity or other daily habits other than the training programme, during the study year. The mean percentage of scheduled sessions attended for

the exercise group was 67%. Twenty-one women from the intervention group and 19 women from the control group completed the whole study year. At the completion of the study, the intervention group showed significant increments in bone mineral density at the Ward's triangle (8.4%, $P < 0.01$) as well as improvement in maximal walking speed (11.4%, $P < 0.001$), and isometric grip strength (9.9%, $P < 0.05$), as compared to the control group. In summary, this combined weight-bearing training programme improved bone density as well as muscle strength and walking ability. (Fig. 11)

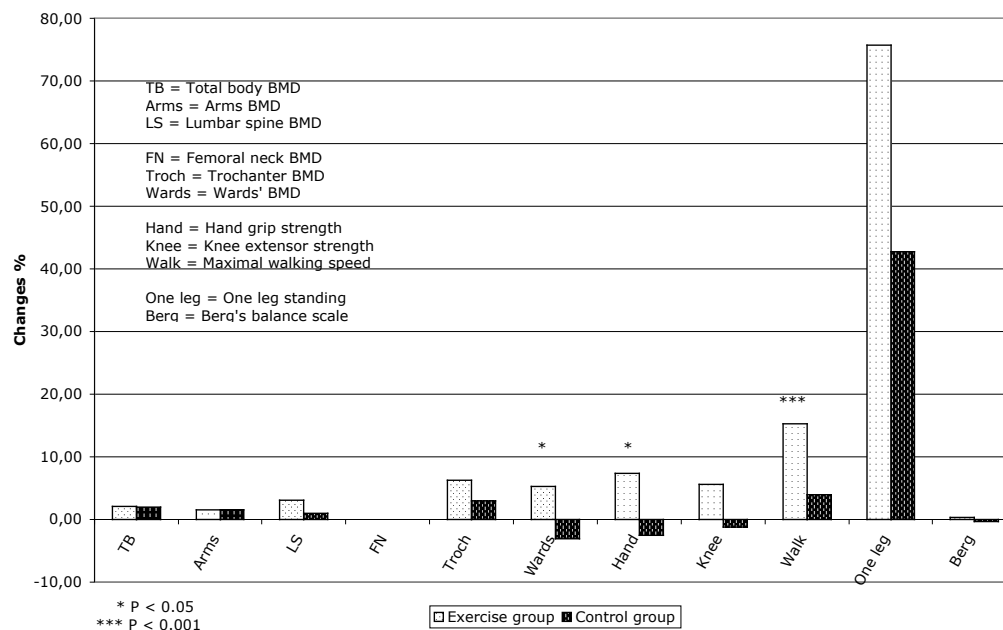


Fig. 11 . Percent changes from baseline to one-year follow up.

Study II

The beneficial effects of exercise on BMD are lost after cessation: a 5-year follow-up in older post-menopausal women

At the follow-up five years after study I was completed, the mean age was 78.6 years (range 73–88) (Flow chart, fig. 10). Both groups

sustained significant losses of BMD at the femoral neck (range –8.1 to –8.5 %), trochanter (–8.3 to –11.9%), and Ward's triangle (–10.6 to –13.6%), whereas there was a significant increase in lumbar spine BMD in the control group (4.8%) together with a significant decrease in height

(-0.6 cm). The increase in lumbar spine BMD for the control group was also significant when compared to the intervention group ($P=0.027$). Nine subjects in the control group were suspected to have new vertebral fractures versus six subjects in the exercise group ($P=0.029$). Both groups also experienced significant decreases based on neuromuscular function tests. The inter-group percentage changes were, however, not significant except for the maximal walking speed where the exercise group showed a greater loss. Three subjects (one from the exercise group and two from the control group) who had continued to be physically active in scheduled training classes at least twice a week showed no loss in BMD or in their neuromuscular performances. In this study,

walking > 210 min/week had no effect on the maintenance of BMD or neuromuscular functions. Fat mass and body weight were significant predictors for the changes in BMD.

There were no significant differences between the groups in levels of β -CTx and osteocalcin and no associations were found between bone turnover markers and level of physical activity. The exercise group had significantly higher levels of total vitamin D in serum than the control group ($93.24 \pm 20.13\text{nM}$, $78.31 \pm 19.48\text{nM}$, respectively). However, the levels were within normal ranges in both groups.

Study III

Physical activity in middle-aged women and hip fracture risk – the UFO study

The mean age at baseline was 57.2 ± 5.0 years and the mean fracture age was 65.4 ± 6.4 years. The controls were significantly more active in berry/mushroom picking. Conditional logistic regression (nested case-control) analyses revealed that the women who were moderate active in leisure activities like gardening and berry/mushroom picking had a decreased risk for hip fracture (OR 0.28; 95% CI 0.12–0.67), compared to the women who were less active. Increased body height enhanced the fracture risk (OR 1.15; 95% CI 1.07–1.23). Commuting activity, occupational physical activity, self-reported training habits at baseline, physical activity in youth, alcohol

habits, menopausal status, and use of hormone replacement therapy was not shown to have any significant influence on the hip fracture risk.

Study IV

Active commuting reduces the risk of wrist fractures in middle-aged women – the UFO study

The mean age at baseline was 54.3 ± 5.8 years and the mean age at fracture was 60.3 ± 5.8. The control group was significantly more active in dancing and snow shoveling, whereas the fracture group was more active in bicycling. The control group's level of commuting activity was also higher than the fracture group's commuting activity. Unadjusted regression analysis showed an increased fracture risk with training in the last three months (OR 1.36; 95% CI 1.00–1.83) and with a high

frequency of bicycling in leisure time (OR 1.58; 95% CI 1.15–2.17), whereas there was a significant risk reduction for snow shoveling and dancing (OR 0.63; 95% CI 0.47–0.85 and OR 0.58; 95% CI 0.35–0.94 respectively). Moderate occupational activity and a high level of commuting activity were associated with reduced fracture risk (OR 0.70; 95% CI 0.51–0.98 and OR 0.55; 95% CI 0.34–0.90 respectively). Multivariate conditional logistic regression analysis with adjustments for height, weight, smoking, alcohol use, and menopausal status showed that subjects with active commuting (especially walking) in the

autumn, winter, and spring seasons had a significantly reduced risk of sustaining a wrist fracture (OR 0.48; 95% CI 0.27–0.88), compared to subjects who commuted by car or bus. The leisure activities snow shoveling (OR 0.50; 95% CI 0.32–0.79) and dancing (OR 0.42; 95% CI 0.22–0.80) also showed significant associations with reduced fracture risk. The increased risk seen with training activity, occupational activity and bicycling in leisure time disappeared when the adjustments were made. Body weight also reduced the fracture risk (OR 0.98; 95% CI 0.96–0.99).

General discussion

Physical activity is known to be beneficial for bone health in adolescence and young adulthood, but the effect of physical activity in middle-aged and older women still remains unclear, and also whether physical activity can prevent future fragility fractures. Intervention studies on premenopausal and younger postmenopausal women have suggested that exercise or physical activity can preserve or even increase bone mass [101-105]. However, no randomised controlled studies on older women with fractures as end point have been done.

In a randomised intervention study (study I) we found that a combined weight-bearing exercise programme was suitable for older

community living women, and was able to maintain and even increase bone density at the region of Ward's triangle, compared to the control group. Low BMD has been shown to be an independent predictor of fracture risk in elderly mobile women [129, 161] and the rate of bone loss has been associated with the risk of fragility fractures [162]. Thus, maintenance of BMD, as seen in the exercise group might be of importance to reduce their future fracture risk.

Although we found a significant increase in Wards' BMD there was no increase in femoral BMD in response to the exercise programme. Still, Ward's triangle is not a good measuring site, since it is derived directly from the DXA measurement, meaning that the site may vary between two

measurements in the same individual. Ward's triangle mainly consists of cancellous bone, which has a higher turnover than cortical bone. This might explain why we found increases in BMD at Ward's triangle, in the exercise group, but not in the femoral neck. Thus the length of the intervention might have been too short to observe a response in the femoral neck. However, there were no significant inter-group differences at the lumbar spine, which would have been expected since this site also has a high content of trabecular bone. In fact both controls and exercisers had a tendency towards increased lumbar spine BMD during the study period, which could be attributable to age-related degenerative processes like spondylosis or even vertebral compression fractures. Thus the

accuracy of the spinal BMD measurements is not very good in the elderly.

Another explanation for the lack of effect in the femoral neck and lumbar spine could be that the programme did not include high impact activities. Thus, the exercise programme was designed to load bones with intermittent compressive forces, introducing atypical and novel stress on the bone, which is known to improve skeletal integrity, but jumping activities were not included as the programme had to be suitable for older women. We assumed that it would have been too difficult to perform jumps for some of the participants. It is thus possible that this training programme, although quite intense for women of this age, but without jumping activities did not create sufficient

strains to evoke an osteogenic response in the femoral neck or the lumbar spine. On the other hand, several other studies, including studies in older postmenopausal women, have not shown any effects of jumping exercises on bone mass either [108-110]. One study even indicated that intensive high impact exercise, such as jumping, may cause a reduction in regional bone mass[109].

Physical activity is also known to be beneficial for neuromuscular functions such as muscle strength, balance and walking ability in old age, and thereby reducing the risk of falling [107, 130, 131]. Thus, the improved walking ability along with the tendency to increased quadriceps muscle strength seen in our study subjects (study I) might contribute to a decreased

risk of falls and subsequent fractures. An earlier study in elderly women indicated an association between quadriceps strength and BMD at the femoral neck and Ward's triangle and lumbar spine [163], but we were unable to verify those findings in our study. However, we measured isometric strength of the knee extensors, whereas a dynamic measurement, as used in the study by Murphy and Wilson, might have been better for the outcome of this type of dynamic exercise [164]. Lean body mass decreased during the intervention period in both exercisers and controls, but the participants in the exercise group still improved their muscle strength and neuromuscular functions. This implies that the effect of the training programme on neuromuscular function may have

been due to neural adaptation rather than muscle hypertrophy [165].

Not surprisingly, there were no maintained effects on BMD or neuromuscular functions detectable five years after cessation of training (study II). Both groups showed a BMD loss equivalent of what is expected for the age group and there were no differences in the level of bone turnover markers. This lack of benefit after cessation of training is in line with a previous study on premenopausal women where the exercise-induced benefits in femoral neck BMD had disappeared one year after the training had stopped [117]. However, another study on premenopausal women showed maintenance of the exercised-induced increments in BMD of

femoral neck, distal femur, patella, proximal tibia and calcaneus 3.5 years after the intervention ceased [118]. In a study on postmenopausal women aged 70–78 years, exercise-induced gain in balance and bone strength were partly maintained one year after cessation of a high-intensity training programme. However, their exercise group did not stop entirely with training after the intervention had ceased [142]. In our study the follow-up time was much longer, wherefore a comparison with other studies of shorter duration is difficult to carry out. Furthermore, the subjects in our study were also older than the women in the majority of the other follow-up studies. Thus, within this group of older women there is normally a decline in neuromuscular performance [127, 128] and both

groups in our study (study II) also decreased their muscle strength, gait speed, and balance over the five years of follow up, which could have blunted any previous effect. Another study by Cao et al showed maintenance of neuromuscular benefits and partly also calcaneal bone effects, measured with ultrasound, six month after cessation of a 12-month exercise and nutritional intervention. Still, these subjects performed continued training of at least 30 min 3 days/week following the end of the intervention [166]. In our study (Study II), only three participants continued with scheduled training classes at least twice a week, but interestingly these three women did not have any decreases in BMD or neuromuscular performance. However, we can only speculate about the

association between the exercise classes and BMD and neuromuscular functions as the group is far too small to base any conclusions from. It should also be added that there might be a remaining anti-fracture effect that was not measurable with the method we used. Thus, it cannot be ruled out that the exercise intervention was associated with residual structural skeletal benefits that were not depicted using a planar method as DXA.

Interestingly, both groups showed increase in lumbar spine BMD at the five-year follow-up (study II). These increments in lumbar spine BMD could partly be explained by degenerative processes in the spine, which are common among older women and give a falsely high BMD. Unfortunately we could not apply to the

recommended method for detecting vertebral compression fractures [44, 45]. Estimations of possible vertebral compression fractures based on the DXA measurements and a significant height loss among the subjects, made us, however, suspect that there were more vertebral compression fractures in the control group (study II), and that the intervention group may have had a reduced propensity for vertebral fractures as a result of the training programme.

Thus, it seems that physical activity is beneficial for bone density and neuromuscular functions even in old age and could therefore have long-term protective effects against fragility fractures. As a paradox, however, physical activity may simultaneously increase the acute

risk of a fall and indirectly the risk of fractures. [61, 139]. There have also been suggestions of a U-shaped association where the most inactive and the most active persons may be at higher risk of falls and fragility fractures [63, 167]. We were, however not able to confirm this U-shaped association in our case-control studies of hip and wrist fracture cases (study III and IV). Thus, in our study hip fractures (study III), women who were moderate active with leisure activities such as gardening and berry/mushroom picking had the lowest hip fracture risk. In a study in women aged 65 years and older, frequent walking was a risk factor for distal forearm fractures, along with number of falls in the past year, low bone mineral density, and poor visual acuity [64]. Among persons aged 70 years and older,

moderately impaired walking ability and going outdoors less than once a week have been associated with a lower risk of distal forearm fracture [63]. In another study of women, aged 45 years and older, women who had difficulties performing physical functions and had lower-extremity problems were also at lower risk of wrist fracture [168]. Thus, all these studies suggest that wrist fractures are less common in inactive women compared to physically active women. Recently, it was suggested that wrist fracture occurs in women with low bone mass who are otherwise in good health and are physically active, but who are somewhat prone to falling, and whose movements are not slowed by lower extremity problems or other debilities [168]. Interestingly, in our study of wrist

fractures (study IV) women who had cycled in leisure time or trained, wearing training clothes during the last three months seemed to be at a higher risk of wrist fractures compared to the sedentary ones. However, after adjusting for other confounding factors, the risk was no longer significant. On the contrary, women performing active commuting, or leisure activities such as dancing and snow shoveling had a reduced risk for wrist fractures. Thus, we were not able to confirm the hypothesis that physically active women are at higher risk of sustaining a wrist fracture. Quite the opposite, physical activity seems to lower the wrist fracture risk in our cohort. These results are in line with the study by Thorpe et al in 1865 peri- and postmenopausal women followed for 25 years,

where there was a 37% reduction in the wrist fracture risk for women with a high level of physical activity compared to women with a low level of activity [65].

Physical activity also seems beneficial for preventing hip fractures. Thus, in our study III, leisure activities such as gardening and berry and mushroom picking were associated with a significant decreased risk for future hip fractures. This is somewhat surprising considering that neither of these activities put a great weight-bearing loading on the skeleton. These activities may, however, challenge neuromuscular functions such as muscle strength and balance and might therefore contribute to maintaining these functions and

subsequently the ability of parrying a fall. The activities are also performed outdoors in the summertime when there is enough sunlight, even in the north of Sweden, to induce the vitamin D synthesis in the skin. The sunlight exposure might have influenced the levels of vitamin D, and thus given the subjects both skeletal and neuromuscular benefits [147-151], thereby preventing them from having falls and fractures. Worth noting in this context is that, in a subcohort of the UFO study, low vitamin D levels were recently found to be a risk factor for hip fracture [158]. Many of the leisure activities, included in the VIP-questionnaire could be seen as markers of an overall physically active lifestyle. Dancing and snow shoveling for example were both associated with a reduced wrist fracture risk

(study IV). Snow shoveling is naturally only performed in the wintertime. Even though it burdens the arms rather heavily and may influence BMD in a positive way, a women who shovel snow is most likely strong and physically fit.

A somewhat surprising result in study IV was the reduced wrist fracture risk seen with active commuting. The highest level of commuting activity was coded as walking to and from the workplace. Walking does not have any loading effect on the arms unless walking poles are used. Even though walking with poles has increased in popularity in the last few years, it was not commonplace when the participants filled in the questionnaire in the 90s. The finding that active commuting in

autumn, winter, and spring reduced fracture risk probably reflects an all year-round physical activity among concerned women. In study III and IV, we did not measure BMD or any neuromuscular variables, but one assumption is that women who were physically active in their leisure time and who walked to their place of work even in wintertime had an overall active lifestyle, which may have resulted in skeletal benefits, and/or increased their muscle strength and improved their balance, thereby reducing their risk factors for falls and fractures. Still these results may seem like a contradiction to the results from study II, where walking at least 210 min per week had no effect on maintenance of BMD or neuromuscular functions. However, the variables and end-

points examined in these studies are not the same. In study II we measured BMD and neuromuscular functions in a rather old group of postmenopausal women, and it seems like in this age group, walking as a form of exercise, was of too low intensity to maintain BMD or neuromuscular functions in a group of women who were quite physically active and independent in their daily lives. Thus, although walking is an activity suitable for many older women, a recent meta-analysis of eight eligible trials showed that walking produced no benefits of BMD in the lumbar spine, while some effects was found in the femoral neck in postmenopausal women (45 years and older)[111]. The women in study IV were younger and were walking to and from work. This type of walking

activity may have been performed with a higher pace and intensity than the older women in study II did. Also, it should be remembered that the end point in study IV was wrist fracture, so we had no knowledge about the subjects' BMD, muscle strength or balance.

Strength and limitations of the studies

The participants in study I and II volunteered because of a genuine interest in physical activity and there was a good attendance to the exercise programme. There could have been some bias because some of the women in the control group were friends with women in the training group, and the members of the control group could thereby have got knowledge about the training program, and not have been as sedentary as they

were supposed to be. This could of course have influenced the results. Major shortcomings of both studies were the small sample sizes and subsequently the low power to detect significant changes in BMD and neuromuscular functions. Moreover there was a drop out rate of 15% to the follow up, which could have influenced the results (study II). As a consequence, it was not possible to study fractures in these studies. Unfortunately we did not have the resources to keep the investigators blinded to which study group the participants belonged. The main strengths of study III and IV are the semi-prospective design where data from cases and controls have been collected under an identical experimental protocol during the same time period, the high participation rate in the health

survey, and the strict criterion for fracture diagnosis. However, the weakness of these studies is that all information about physical activity and other lifestyle variables are self-estimated and self-reported. The questionnaire was originally developed to investigate risk factors for diabetes and cardiovascular diseases and not osteoporosis or fragility fractures [169]. We therefore had to recode the physical activity variables to be suitable in the statistical analysis. The assessments of the different activities were crude and we had no estimation on the intensity or duration of the activities or the loading characteristics. Due to the study design we do not know whether the subjects kept the same activity level during the whole follow-up time, which also differs among the individuals.

Other important confounding factors, such as disease status, weight, use of drugs etc. may also have changed during that time. It should also be noted that the subjects in study III were much younger than the average hip fracture patient in Sweden so these women may not be representative for the usual hip fracture patient. We do not know if these women were healthier than the average hip fracture patient because they were younger, or if they were at poorer health and therefore more prone to sustain a hip fracture at a younger age.

Ethical considerations

In 1995 treatment for osteoporosis was not common practice yet, and the subjects randomised into study I were therefore not further examined or

treated if they had osteoporosis. However, when the participants were followed up in 2001, all subjects who had osteoporosis at any measured site were referred for further examination and treatment. The women were also referred for further examination if their health check up revealed any abnormalities as regards to the general blood tests. All participants in study III and IV had previously donated blood samples and data about their lifestyle and given their written consent to use these data for medical research purpose as part of the VIP study. Given that some of the subjects had deceased years after they gave their consent to the VIP study, information about the UFO study was given in the local newspapers in June 2006 to notify subjects who were still alive

and relatives of the deceased about the purpose of the study.

Clinical implications

The first study in this thesis has shown skeletal but preferentially neuromuscular benefits from a combined weight-bearing exercise programme for older women. The study also imply that a combined weight-bearing programme is suitable for older women and may have a propensity to influence the risk factors for falls and fractures in a positive way. However, the physical activities have to be carried on in order not to loose the exercise-induced benefits. Walking is often recommended as an activity for older women to maintain bone density and reduce fracture risk factors. Yet, in our first study on older women (73-88 years), walking did not influence bone density or neuromuscular

functions. However in the cohort of middle-aged women, walking as a commuting activity seemed to lower the wrist fracture risk, whereas leisure activities performed outdoors, such as gardening and berry- and mushroom picking lowered the risk of hip fractures. In summary, an overall active lifestyle in postmenopausal women seems to be beneficial for bone health and may prevent fractures. The present studies indicate that sedentary middle-aged and older women should be encouraged to increase their physical activity, especially their outdoor leisure activities, in combination with some weight-bearing high-intensity activity in order to improve muscle strength, balance and possibly BMD, to reduce their risk of falls and fractures.

Implications for future research

The results from study III and IV pertained to middle-aged women who were not very old when they fractured. Since we do not know if they will maintain their physical activity up into older age or how the activities influence their fracture risk as they get older, it would be of outmost interest to follow the cohort further and analyse the influence of physical activity on the fracture risk in the ages over 80. The best way to study the effects of physical

activity on risk factors for falls and fractures would of course be in randomised blinded trials, but for methodological reasons such trials are almost impossible to perform.

The risk for men to sustain a fragility fracture is about half that of women, but we do not know if our results are applicable to men as well. Further research on both men and women is necessary to enlighten this multi-factorial area of fragility fractures, and to give evidence-based recommendations to the population.

Conclusions

A combined weight-bearing training programme is suitable for older community living women, and might improve bone density as well as muscle strength and walking ability, thereby having the propensity to reduce risk factors for falls and fractures.

The positive effects for older women on bone mineral density and neuromuscular functions achieved by a combined weight-bearing programme are lost after cessation of training. Walking did not have enough power to influence neuromuscular functions or bone density at the hip. Continuous high-intensity weight-loading activity is probably necessary to preserve bone density and neuromuscular functions in older women.

A physically active lifestyle, with outdoor activities, in middle age is associated with reduced risk of both hip and wrist fractures. Possible mechanisms may include sunlight exposure from outdoor activities, together with improved muscle strength, coordination, and balance, resulting in a decreased risk of falling, and perhaps also direct skeletal benefits.

A physically active lifestyle from childhood through to old age may have the potential to prevent fractures in elderly women. However, as a comfort to sedentary women: it is never too late to begin being physically active but it is always too early to stop training.

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