THE ROLE OF PHYSICAL ACTIVITY ON BONE DENSITY AND BONE GEOMETRY IN MEN

Martin Nilsson

UNIVERSITY OF GOTHENBURG

Institute of Medicine at Sahlgrenska Academy,
University of Gothenburg, Gothenburg, Sweden,
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Till minne av mina älskade föräldrar.

To get back my youth I would do anything in the world, except take exercise…...

Oscar Wilde, The Picture of Dorian Gray

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ABSTRACT

Introduction: Several studies indicate that peak bone mass, reached during the third decade in life, is an important determinant of osteoporosis later in life. Physical activity with dynamic loading of the bone is an important determinant of peak bone mass. Exercise especially before and during puberty is associated with increased bone density and cortical bone size in children and young adults. It has, however, not been established for how long this alteration will remain if the level of physical activity is decreased or ceased. Furthermore, the previously used technology in measuring bone mass has not been able to explain how physical activity influences bone microarchitecture that can affect bone strength and resistance to fracture in humans.

Objective: The overall aim of this thesis was to gain a better understanding of the role of physical activity and inactivity on bone density, bone geometry, and trabecular microarchitecture in men.

Methods: Four large and representative cohorts, three with young adult men and one with elderly men, were used in these population-based, cross-sectional studies. Data concerning physical activity was collected using standardized questionnaires. Bone parameters were assessed using dual-energy X-ray absorptiometry (DXA) for areal bone mineral density, peripheral quantitative computerized tomography (pQCT) for volumetric bone mineral density and bone geometry, and high resolution 3D pQCT for trabecular microarchitecture.

Results: In a large cohort of young adult men (age 18, n=2,384), history of physical activity was the strongest predictor of calcaneal bone mineral density. Calcaneal bone mineral density was also higher in those who had ceased to be active compared to those who had always been inactive. In a cohort of young physically inactive men (age 19, n=367), previous sport activity was independently associated with cortical bone size of the tibia at the age of 19 years. Subjects, who ceased their sport activity for up to 6.5 years previously, still had larger cortical bone size of the tibia than always inactive subjects. In a large cohort of elderly men (n=498), we found that high frequency of competitive sports during the first three decades in life was independently associated with bone mineral density at several bone sites at the age of 75 years. In a large sample of young adult men (age 24, n=829), we found that the degree of mechanical loading due to type of present physical activity independently predicted trabecular volumetric bone density and trabecular number and that duration of previous physical activity independently predicted cortical cross-sectional area in the tibia.

Conclusions: The findings in this thesis indicate that physical activity during growth plays an important role in the enhancement of peak bone mass and bone geometry even though physical activity is ceased, suggesting that physical activity during growth confers a lasting positive effect on bone and can contribute to the prevention of bone loss in men. We also demonstrated that the degree of mechanical loading due to type of present physical activity was predominantly associated with trabecular microstructure in weight-bearing bone.

Keywords: bone mineral density, bone geometry, trabecular microarchitecture, physical activity, men

BETYDELSEN AV FYSISK AKTIVITET FÖR BENTÄTHET OCH BENGEOMETRI HOS MÄN

Martin Nilsson
Institutionen för medicin vid Sahlgrenska Akademin,
Göteborgs universitet, Göteborg, 2010

SVENSK SAMMANFATTNING

Introduktion: Många studier visar på att maximal benmassa, som uppnås mellan 20 och 30 års ålder, har stor betydelse för risken att drabbas av osteoporos senare i livet. Fysisk aktivitet med dynamisk belastning av skelettet har stor inverkan på den maximala benmassan. Träning, i synnerhet innan och under puberteten, är associerad med ökad bentäthet och ökad kortikal benstorlek hos barn och unga vuxna. Det har dock inte kunnat fastslås hur länge denna förändring kan bevaras om den fysiska aktivitetsnivån reduceras eller upphör helt. Tidigare använd teknik för att mäta benmassan hos människor har heller inte kunnat förklara hur fysisk aktivitet påverkar benets mikroarkitektur, vilket i sin tur kan påverka skelettets hållfasthet och motståndskraft mot frakturer.

Syfte: Det övergripande syftet med denna avhandling var att uppnå en bättre förståelse för vilken roll fysisk aktivitet respektive inaktivitet har på skelettets täthet, geometri och trabekulära mikroarkitektur hos män.

Metod: Fyra stora och representativa kohorter, tre bestående av unga vuxna män och en av äldre män, användes i de populationsbaserade tvärsnittsstudier som ingår i avhandlingen. Data rörande fysisk aktivitet insamlades med hjälp av standardiserade frågeformulär. Benparametrar undersöktes med hjälp av dubbelfotonröntgen absorbtiometri (DXA) för areell bentäthet, perifer kvantitativ datortomografi (pQCT) för volymetrisk bentäthet och bengeometri, samt högupplöst pQCT för trabekulär mikroarkitektur.

Resultat: I en stor kohort med unga vuxna män (18 år, n=2384), var tidigare idrottsaktivitet den starkaste prediktorn för bentätheten i calcaneus (hälbenet). Bentätheten i hälbenet var också högre hos dem som slutat idrotta jämfört med dem som aldrig hade idrottat. I en kohort med unga fysiskt inaktiva män (19 år, n=367), var tidigare idrottsaktivitet oberoende associerad med kortikal benstorlek i tibia vid 19 års ålder. Män som slutat sin idrottsaktivitet för upp till 6,5 år sedan hade fortfarande större kortikalt ben i tibia jämfört med dem som aldrig hade idrottat. I en stor kohort med äldre män (n=498), fann vi att utövande av tävlingsidrott tre eller fler gånger per vecka under livets första 30 år var oberoende associerat med bentäthet i flera delar av skelettet vid 75 års ålder. I en stor kohort av unga vuxna män (24 år, n=829), fann vi att graden av mekanisk belastning beroende på typ av nuvarande idrott var en oberoende prediktor för volymetrisk bentäthet och trabekulärt antal samt att år av tidigare träning var en oberoende prediktor för kortikal tvärsnittsarea i tibia.

Slutsatser: Fynden i denna avhandling indikerar att fysisk aktivitet under uppväxten spelar en viktig roll i förbättringen av den maximala benmassan och bengeometrin även om den fysiska aktiviteten har upphört. Detta tyder på att fysisk aktivitet under uppväxten medför en varaktig positiv effekt på skelettet och kan bidra till att förebygga benförlust hos män. Vi visar även att graden av mekanisk belastning beroende på typ av nuvarande fysisk aktivitet var det som i första hand var associerat med trabekulär mikroarkitektur i tibia.

LIST OF PUBLICATIONS

This thesis is based on the following papers that will be referred to by their Roman numerals:

I **Physical Activity is the Strongest Predictor of Calcaneal Peak Bone Mass in Young Swedish Men**
Pettersson, U.*, Nilsson, M.*, Sundh, V., Mellström, D., and Lorentzon, M.
*Contributed equally to this work
Osteoporosis International. 2010 Mar; 21(3):447-55

II **Previous Sport Activity during Childhood and Adolescence is Associated with Increased Cortical Bone Size in Young Adult Men**
Nilsson, M., Ohlsson, C., Mellström, D., and Lorentzon, M.
Journal of Bone and Mineral Research. 2009 Jan;24(1):125-33

III **Competitive Physical Activity Early in Life is Associated with Bone Mineral Density in Elderly Swedish Men**
Nilsson, M., Ohlsson, C., Eriksson, AL., Frändin K., Karlsson, M., Ljunggren, Ö., Mellström, D., and Lorentzon, M.
Osteoporosis International. 2008 Nov;19(11):1557-66

IV **Association of Physical Activity with Trabecular Microstructure and Cortical Bone at Distal Tibia and Radius in Young Adult Men**
Nilsson, M., Ohlsson, C., Sundh, D., Mellström, D., and Lorentzon, M.
Journal of Clinical Endocrinology & Metabolism [Accepted for publication]

CONTENTS

LIST OF ABBREVIATIONS

aBMD	areal bone mineral density
ANOVA	analysis of variance
BMC	bone mineral content
BMD	bone mineral density
CI	confidence interval
CSA	cross-sectional area
CT	computed tomography
DXA	dual-energy X-ray absorptiometry
GOOD	Gothenburg Osteoporosis and Obesity Determinant
HR-pQCT	high-resolution peripheral quantitative computed tomography
MrOS	Osteoporotic Fractures in Men
OI	osteogenic index
PC	periosteal circumference
pQCT	peripheral quantitative computed tomography
SD	standard deviation
SPSS	Statistical Package for the Social Sciences
vBMD	volumetric bone mineral density
WHO	World Health Organization
µSv	microsieverts

INTRODUCTION

General introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone density and micro architectural deterioration of bone tissue, with a consequent increase in bone fragility and fracture risk in both men and women (1). It has been demonstrated that bone mineral density (BMD), a surrogate measure of bone strength, is a primary determinant of fracture risk in the general population (2). The risk of developing osteoporosis is determined both by the maximum attained bone mass, peak bone mass, early in life and the subsequent bone loss with aging (3-5). Although genetic factors most importantly regulate both theses processes, physical activity with mechanical loading has the ability to considerably augment peak bone mass, but also to reduce age-dependent bone loss (6-11).

Scandinavian women and men have among the highest risk of osteoporosis-related hip fractures in the world (12). The lifetime risk of osteoporosis-related fractures today is 50% for women and 25% for men (13) and the risk has at least doubled since 1950 in both sexes (14). Hip fracture causes the greatest morbidity and mortality out of all osteoporosis related fractures and almost 30% of all hip fractures occur in men (15). Recent studies have found that osteoporotic fractures, and especially hip fractures, in men result in higher mortality than those in women (16-18). About 20% of women and 30% of men do not survive the first year following a hip fracture (17-20). In addition to its ability to predict fractures, BMD has also been shown to be a predictor of survival, especially in older subjects (21, 22).

The risk of osteoporosis related fractures increase with age. Hence, the aging population contribute to the increased incidence (23). However, also the age-specific incidence has been found to increase in the urban but not in the rural population, suggesting that aging can only partly explain the increasing fracture incidence (24, 25). An environmental factor like mechanical loading has a major impact on the development of bone mass (26, 27). Therefore, a change towards an urban lifestyle, associated with less physical activity, could be another important determinant of the increased incidence in osteoporosis-related fractures.

The World Health Organization (WHO) has, based on measured bone mineral density, proposed a classification for the definition and gradation of osteoporosis in women (28). Some data indicates that the relationship between the level of bone mineral density and fracture risk is the same in women and men (29). However, there is still lack of applicability to diagnose osteoporosis in men. Although we have witnessed a considerable increase in our understanding and management options for osteoporosis in men, there are a number of important gaps in our knowledge (30). One of these gaps is to clarify the role of physical activity in the chain of possible and important factors to prevent male osteoporosis.

The conventional method to diagnose osteoporosis, using dual-energy X-ray absorptiometry (DXA), does not directly measure all elements that may contribute to bone strength. BMD assessed with DXA result in a two dimensional projection of the bone, areal bone mineral density, but does not give any direct information about the volumetric density, geometry, and microarchitecture of the bone. The mechanical strength of the bone and resistance against fracture is believed to be dependent on bone geometry, volumetric density (31, 32) and microarchitecture (33).

Skeletal physiology

The skeleton is a complex living tissue that fulfils several functions. It serves as an internal supporting structure to the whole body, protects the inner organs, and enables the body to move by being an attachment for muscles and ligaments. To optimize these functions and to secure the strength when exposed to strain, the bone tissue is both hard and elastic at the same time. Furthermore, the skeleton is a metabolic organ serving as a major reservoir of calcium, phosphate, and other ions (34, 35).

Skeletal anatomy

Anatomically the skeleton consists of three main types of bone, based on general shape. There are flat bones such as the skull, sternum, ribs, and scapula, short bones represented by the vertebras, included in the axial skeleton, and some bones in the hand and foot, as well as long (tubular) bones such as the femur, tibia, humerus, and radius (34, 35). The flat bones, included in the axial skeleton, serve as armor for the vital organs they surround. Both the long and short bones serve as levers for the muscles supporting locomotion and other forms of motion (34).

Bone cells

Bone is mainly composed of living cells, extracellular matrix, water and lipids (26, 35, 36). The extracellular matrix is a composite of 20-40 % organic material, with collagen fibrils that are tough and elastic, and 50-70 % inorganic material, with minerals that gives the tissue hardness and rigidity. There are three major living cells that control the structure of the matrix and the regulation of skeletal turnover: osteoblasts, osteoclasts, and osteocytes (26, 35, 36). Osteoblasts, cells of mesenchymal origin, are bone forming cells that produce the bone matrix. Osteoclasts, multinucleated cells of hematopoietic origin, is the only cell that can resorb bone tissue, resulting in a release in calcium to the circulation. Osteocytes are the most abundant cell type of bone and represents the terminal differentiation stage of the osteoblasts and are embedded within the bone (26, 35, 36). They are connected by canaliculi, of unmineralized matrix, and are thought to function as mechanosensors when the bone is exposed to mechanical loading (26, 35, 36).

Bone remodeling

Bone remodeling is characterized by an ongoing maintenance of bone tissue dependent on the levels of stress the bone is exposed to (27, 36). This continuous remodeling process takes place on all skeletal surfaces in basic multicellular units (also known as "bone metabolic units"), which are small areas where osteoclasts and osteoblasts work together in a special sequence to replace old or damaged bone tissue (27, 36). Bone remodeling is known to have two major functions. The first is to be the preventive maintenance of mechanical strength by unceasingly replacing fatigued bone by new; and the second is the important role in mineral homeostasis by making the skeletal stores of calcium and other minerals accessible (34).

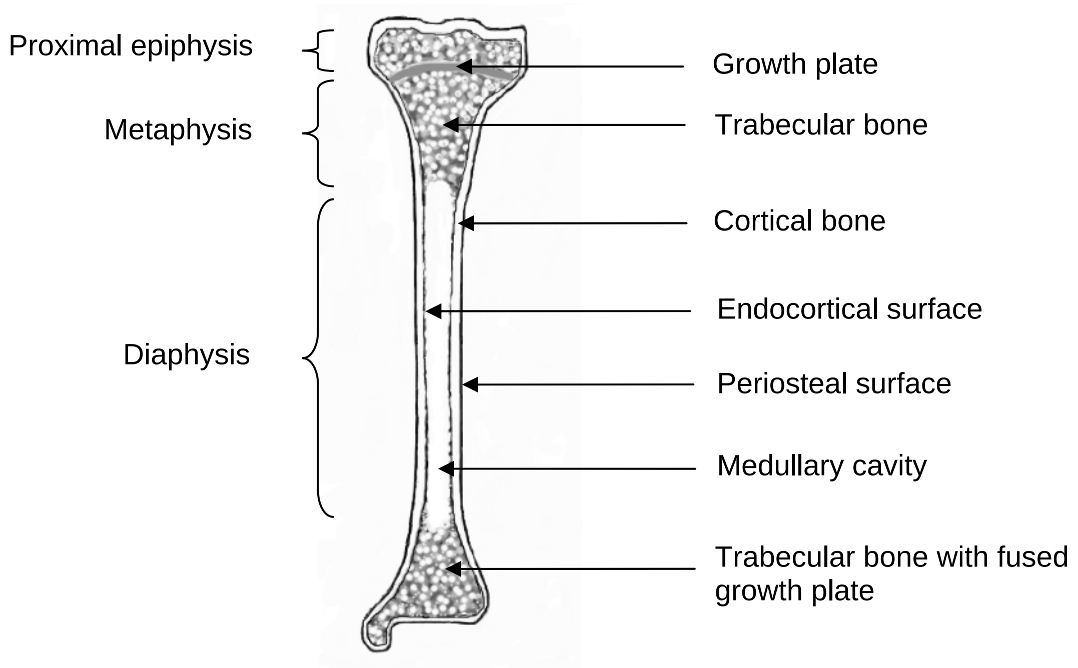

Figure 1*. Schematic view of a longitudinal section through a long bone (tibia).*

Long bones, also known as the appendicular skeleton, are built up of a hollow tube (diaphysis) that flares at the ends to form a bulb-like shape including the metaphysis and epiphysis (Fig. 1) (34, 35). During growth, the metaphysis and epiphysis are also divided by the growth plate that closes during the end of puberty (27, 34). The skeleton is built up by two different forms of bone: cortical (compact) bone that mainly serves as a mechanical and protective outer layer and the inner region of trabecular/cancellous (spongy) bone which is generally considered to have a higher metabolic activity and covers totally a larger surface area than the denser cortical bone (34, 35). The diaphysis consists primarily of cortical bone, while the metaphysis and epiphysis comprise trabecular bone surrounded by a shell of cortical bone (Fig. 1) (34, 35). The adult human skeleton is composed of about 80% cortical and 20% trabecular bone, but the relative proportion of the two types of bone vary substantially between different skeletal sites. To mention a few, the ratio of cortical:trabecular bone is estimated to be about 25:75 in the vertebrae, 50:50 in the femoral head, and 5:95 in the diaphysis of the radius (34).

Peak bone mass

The human skeleton is characterized by a constant change through out life that could roughly be divided into a modeling phase followed by a remodeling phase. During childhood and adolescence an enormous development of the skeleton occurs when more than 90% of adult bone mass is acquired (37). The modeling phase during growth refers to alterations in the shape of the bone. This process is most easily to understand in the long bones where both a longitudinal and radial alteration occur (27). Longitudinal growth is achieved by bone formation at the growth plates in both ends of the bone (Fig. 1) (27). The lengthening of the bone is accompanied by periosteal apposition which increases the diameter, while a simultaneous endosteal resorption of the cortical bone excavates the medullary cavity (Fig. 1) (27, 38). The endocortical resorption is exceeded by periosteal apposition resulting in a wider and wider cortex together with a thickening of the cortex during puberty (38).

The cortical bone apposition is sex specific. Pubertal androgen production in boys increases periosteal apposition and cortical thickness, while estrogens in girls contributes to earlier inhibition of periosteal bone formation as well as completion of longitudinal growth producing a smaller diameter and shorter bone (38-40). During early puberty, an increase in bone size predominates, while there is very little increase in volumetric BMD in both girls and boys (41, 42). During later stages of puberty, trabecular and cortical vBMD increases because of bone mineral accrual (41, 42). The maximum level of bone mass, peak bone mass, is reached somewhere between the end of the second decade and the end of the third decade in life dependent on studied bone site (43-49). In addition to the growing years, bone modeling can occur under other circumstances, such as exposition to high mechanical loading (50), but after attainment of peak bone mass, bone remodeling is the predominant phase.

The peak bone mass has been estimated to account for about one half of the variation in bone mass until 65 years of age (3, 4). Although genetic factors are the strongest determinants of peak bone mass (5, 8, 10), an environmental factor like mechanical loading also has a major impact (7, 11, 51). Several studies have indicated that peak bone mass is an important determinant of osteoporosis later in life (3-5). Therefore, small gains during attainment of peak bone mass may be of importance in preventing osteoporosis.

Age related bone loss

After the attainment of peak bone mass there is a progressive loss of bone (3, 4, 37, 52). The age related bone loss can be attributed to a number of age related factors including malnutrition, reduced levels of sex hormones, heritability, inactivity, medications, and diseases causing secondary osteoporosis (53, 54).

When the loss of bone starts in men, they lose approximately 1% of their bone mineral density per year as they age (55). This pattern of gradual loss of bone density is sex specific. The early postmenopausal years are associated with accelerated loss, especially of trabecular bone, followed by more gradual but sustained loss of bone density (26). Bone mass and density determined by DXA is areal and can be confounded by differences in bone size. Recent cross-sectional and longitudinal studies, using techniques measuring volumetric bone mineral density, geometry, and microstructure, have shown that trabecular bone loss already begins in young adult life, whereas cortical bone loss begins after midlife in men (56, 57). However, the trabecular bone loss was found to be site specific, and started before midlife at the spine, distal radius, and distal tibia, while the trabecular loss continued at the spine but was attenuated at the distal radius and distal tibia in older men (57). Even though the cortical volumetric bone mineral density is reduced in older men, the periosteal apposition continues throughout life. This process is more pronounced in men than in women, further augmenting the sex-specific differences in cortical bone size, in favor of the men. In contrast, the endosteal side of the cortical bone has shown a greater resorption than the periosteal apposition, resulting in a net decrease in cortical area (56). Even though the cortical area is reduced the strength of the bone and resistance to bending forces are compensated by maintained periosteal apposition (39)

Biomechanics of bone

When mechanical forces are applied to the bone a deformation (strain) of the bone tissue will occur, resulting in an internal resistance (stress) to the applied force (36, 58, 59). This internal resistance is equal in magnitude, but opposite in direction, to the applied force and is distributed over the cross-sectional area of the bone (36, 58, 59). The highest stresses in the appendicular skeleton are often caused by bending and torsional loading. Therefore, resistance against these types of loading is of great importance to avoid fracture. In a tube like construction as the appendicular bones, the most efficient geometrical design for resisting forces from bending and torsional loading involves a distribution of the material away from the center of the bone (36, 58). The resistance of bone to bending and torsion forces is related exponentially to its diameter which makes the size of the bone an important contributor to bone strength (32). This means that even small increases in the outer circumference of a bone could make a substantial contribution to its strength and fracture resistance (32).

Trabecular bone architecture has also been found important in terms of bone strength. A two dimensional finite element model using human specimen of bone (60) together with computer generated models using three dimensional reconstructions of trabecular bone architecture (61) have shown that loss of trabeculae is of greater importance for the bone strength rather than reduced trabecular thickness. At a given decrease in bone density reductions of trabeculae decreased bone strength two to five times more than reductions in trabecular thickness. Findings were similar for loading in both transverse and longitudinal direction (60). This means that it is important to maintain trabecular number in order to preserve bone strength with aging.

Osteoporosis

The diagnostic criteria for osteoporosis was established by the WHO in 1994 and based on bone mineral density (BMD) T-scores in women, but not in men or children (28). The T-score expresses a patient's BMD as the number of standard deviations (SD) by which it differs from the mean peak value in a reference population of young, healthy adults of the same sex in the same population (62). A threshold below 2.5 SD below the mean of young adults of the same sex is used as the criterion for a diagnosis of osteoporosis. Furthermore, a threshold of more than 1.0 SD but less than 2.5 SD below the reference mean is the criterion for a diagnose of osteopenia (low bone mass). If BMD is more than 2.5 SD below the reference mean and the individual has had one or more osteoporosis-related fractures, the patient is diagnosed to have established osteoporosis (28). Although these criteria for diagnosis were developed for women, the presence of reduced BMD in men is commonly quantified with T-scores using a grading system parallel to that used in women (30). Whether this reference range used in women, or male-specific reference range, should be used in diagnosing osteoporosis in men has been controversial (30). However, research has shown that BMD measures can be at least as effective in men as in women in predicting future fracture risk (62).

Risk factors for osteoporosis-related fractures

BMD measured by DXA is a surrogate measure of bone strength and is the primary determinant of fracture risk in both men and women (63, 64). Every standard deviation decrease in BMD is associated with a three-fold increase in the age adjusted hip fracture risk in postmenopausal women, and with a three-fold risk increase in elderly men (29, 65). Several other interacting factors contribute to the risk of osteoporosis-related fractures, and may also exert their effects through BMD. Heredity is the far most important factor in both women and men, where family studies and studies of monozygotic and dizygotic twins have shown that genetic factors can explain up to 80% of the variability in bone mass (5, 10, 66-70).

Risk factors for osteoporosis are divided into those that can be modified and those that cannot be modified. Where age, heredity, previous fragility fracture, parental history of fragility fracture, female gender, and early menopause are the most important osteoporosis-related risk factors that cannot be modified. The most important risk factors that can be modified and is related to lifestyle are smoking, sedentary lifestyle, low body mass index, diet lacking in calcium, high alcohol consumption, and low levels of vitamin-D due to lack of sunlight exposure or malnutrition (62). Certain medical conditions and medications like long use of corticosteroids, rheumatoid arthritis, over-active thyroid or parathyroid glands, coeliac disease and other chronic gut conditions, and chronic liver or kidney disease can cause secondary osteoporosis (26, 54, 62).

Physical activity and bone mass

Physical activity is an important factor in skeletal development and can prevent and treat age-related reductions in bone strength due to the inherent sensitivity to mechanical loading in bone tissue. When the skeleton is exposed to altered levels and patterns of mechanical loading the bone tissue responds by an adaptive mechanism called the mechanostat hypothesis, by analogy with a thermostat, based on "Wolff's Law" (71, 72). Wolff's law, presented in 1892, summarize the ideas that mechanical influences can affect both internal architecture and external conformation of the bone according to mathematical laws (72). This mechanical and functional adaptation has its origin in the skeletons inherent striving to optimize its strength and architecture according to environmental load bearing conditions the individual is exposed to. In other words, the bone strength and resistance against fracture is increased with increased demand and decreased with lesser demand (36). This continuously ongoing strive to adapt reflects a contradictory process of physical laws and shows the unique feature of the skeleton, especially long bones, in fulfilling the purpose to make movement easier. The skeleton must be as strong and flexible as possible to prevent fracture when the environmental demands increase and at the same time as light as possible to facilitate mobility (38). Perhaps the most convincing evidence that mechanical loading is important for bone adaptation comes from studies of the skeleton put in a state of disuse, i.e. bed rest, spaceflight or spinal cord injury. These studies demonstrate that bone loss is rapid and large when mechanical loading forces acting on the bone tissue are remarkably reduced (73, 74).

The adaptive response to mechanical loading is highly site specific; only those bones that are actually loaded will adapt. This has been shown in several studies in racquet sport players, where the arm holding the racquet had significantly greater bone mass and size than the contra lateral non-playing arm (51, 75-77). Physical activity that involve lifting or pushing your own body weight, weight-bearing loading, has also been found more effective than non weight-bearing activities like swimming and bicycling in the enhancement of bone mass (78-83). Several studies on both men and women suggest that the type of physical activity and the accompanying dynamic activity are of particular importance (84-86). These findings have been supported by animal studies showing that the rate of bone formation is enhanced when the loading is applied dynamically and not with static loading (50, 87). The maximum effect of exercise is believed to be achieved by weight-bearing activities including high magnitude, high frequency, and unusual distribution (i.e. jumping actions, explosive actions like turning and sprinting) and fairly few repetitions rather than endurance or non weight-bearing activities (78, 81, 88-90). The anabolic potential is found to be increased when rest periods are inserted between the mechanical loading events (91). High impact forces on lower extremities caused by drop landings have been found particularly important in the enhancement of loaded bone sites during growth (92-94). During jumping actions ground-reaction forces reach 6-8 times body weight in lower limbs and up to 10-15 times body weight generated by some gymnastic exercise. In contrast, ground-reaction forces during walking or running reaches only 1-2 times body weight in corresponding bone sites (95).

Physical activity appears to play an important role in maximizing peak bone mass and decrease the age-related bone loss (6, 9). However, the young and growing skeleton seems to be more adaptive to the mechanical load applied to it than the older skeleton (51, 96). One report has found that the connectivity of osteocytes, functioning as mechanosensors, is markedly deteriorated with age (97). The authors speculate that this may contribute to the progressive loss of sensitivity of bone tissue to mechanical loading in the aging skeleton, but the association is not yet clear (97). In addition, the ability to perform the needed dynamic and high impact loading could be limited in older adult persons due to the associated risk for injuries and fractures (98). As a consequence, studies on the effect of physical activity on the older skeleton have mostly involved activities with high intensity but low or moderate impact loading, i.e. walking, running, stair climbing, resistance training, aerobics, weight training, and dynamic balance.

It is well known that physical training before and during puberty is of great importance to increase bone density (6, 51, 85, 96, 99, 100) and bone geometry (75, 85, 101) in both girls and boys. One study reported that racquet sport players who began to play before and in early puberty had more than twofold greater difference in bone mineral content between their playing and non-playing arm compared with those who began their playing career after puberty (51). If the exercise is performed during late adulthood a decreased bone loss or a smaller increase in bone density could occur (102). However, results from studies of the effect of exercise on bone mass in adult persons are somewhat inconsistent. Both resistance training and impact loading have a positive effect on bone mass, especially at the lumbar spine, in both pre- and postmenopausal women (103-105). In contrast, regular walking has no significant effect on BMD at the spine, but a positive effect at femoral neck, in postmenopausal women (106). Studies conducted in postmenopausal women using pQCT reported benefits of training on cortical components at distal and shaft sites of loaded bone segments rather than trabecular components of bone (107). The effects of training in postmenopausal women appear to be modest, but exercise is capable of modifying bone mass and geometry in a way that may improve bone strength (107). Furthermore, the most substantial changes in bone mass and geometry were found in response to high-impact loading activities, i.e. volleyball and jumping, in agreement with findings in younger persons. Measurements done by pQCT were better to identify effects of exercise on bone than DXA measurements when both techniques were used (107).

Even though exercise is found beneficial for bone health during growth it is still debated whether the benefits on bone structure and density of physical activity early in life will be maintained with reduction in activity level (96). The clinical importance of these exercise induced skeletal benefits could also be questioned if the benefits are not maintained into late adulthood, when fractures occur. Some studies demonstrate that the benefits of physical activity are lost after its cessation (108, 109). In contrast, several other studies have shown that the benefits of previous training will remain when the level of activity is decreased, but also after complete cessation of training (6, 110-116). In the large majority of studies, bone properties have been measured using DXA (6, 110-114). Bone density measured by DXA is areal and can be confounded by differences in bone size, and cannot determine whether changes in areal BMD are due to bone volumetric mineral density (vBMD) or in bone geometrical parameters (117). Therefore, it is possible that studies that have observed bone mass by DXA reflects parallel changes in bone size rather than changes in trabecular or cortical vBMD.

AIMS AND HYPOTHESES OF THE THESIS

The overall aim of this thesis was to gain a better understanding of the role of physical activity and inactivity on bone density, bone geometry, and trabecular microarchitecture in men. The specific aims of the thesis were the following:

I) To determine if physical activity during growth was associated with peak calcaneal bone mineral density in a large cohort of young adult men, highly representative of the young adult male population (Paper I).
We hypothesized that young adult men who were physically active during growth and adolescences had higher calcaneal peak bone mineral density than men of the same age who had never been physically active.

II) To investigate if physical activity during growth was associated with cortical bone geometry in currently inactive young adult men (Paper II).
We hypothesized that young adult men who previously had been, but ceased to be, physically active during growth had greater tibial cortical bone size than men of the same age who never had been physically active.

III) To determine if physical activity early in life was associated with areal bone mineral density in elderly men (Paper III).
We hypothesized that elderly men who were active in competitive sports early in life had higher areal bone mineral density than men of the same age who did not participate in competitive physically activity during the same time period.

IV) To investigate if present and previous physical activity were associated with trabecular microstructure and cortical bone geometry in weight-bearing bone in young adult men (Paper IV).
We hypothesized that type of present physical activity was associated with trabecular microstructure, while number of physically active years was associated with cortical cross sectional area of the tibia in young adult men.

MATERIALS AND METHODS

Subjects

In this thesis four large and representative cohorts, three with young adult men and one with elderly men, were studied. The cohort for paper I was a highly representative sample of young men from the south-west part of Sweden. For papers II and IV, two cohorts of young males from Göteborg were used. In paper III, a cohort of elderly men from Göteborg was used.

Table 1. Characteristics of the subjects in the four studied cohorts. Values are given as means ± SD.

	Paper I	Paper II	Paper III	Paper IV
Number of subjects	2384	390	498	829
Age (years)	18.3 ± 0.3	19.0 ± 0.6	75.2 ± 3.3	24.1 ± 0.6
Height (cm)	180.4 ± 6.7	181.5 ± 6.7	175.9 ± 6.4	182.1 ± 6.7
Weight (kg)	73.6 ± 11.3	73.1 ± 13.2	81.4 ± 12.2	78.5 ± 12.6
Smokers (%)	11.5	14.8	9.2	7.2

Paper I

The subjects were men in a large population-based screening program of physical capacity, cognitive function, and muscle strength in young men as part of the normal compulsory military service in Sweden. The National Service Administration in Gothenburg covers the regions of the south-west part of Sweden, with two million inhabitants, and examines around 10,000 conscripts each year. Between November 1998 and May 2000, every fifth male conscript attending this service administration was randomly selected and asked for participation in the present bone study. In total, 95% of the contacted study subject candidates agreed to participate, and 2,805 males (age, 17.3–19.9 years) were included in the study. All subjects performed mandatory tests for selection to compulsory military service. These tests included measurements of anthropometrics, muscle strength, and physical capacity. As part of this study, these subjects also underwent a BMD measurement of the calcaneus. Complete data on present and former physical activity habits and all covariates was not available for 421 subjects, leaving 2,384 subjects for further analysis in paper I (Table 1).

Height and weight were measured using standardized equipment. A standardized questionnaire was used to collect information about smoking habits, dietary intake, and medical history. Calcium intake in mg/day was estimated from dairy product intake of milk and cheese.

Total and simultaneous isometric muscle strength of the legs, hips, back, and arms were measured in Newton meters (Nm) using an IsoKai machine (IsoKai, M.Produkter, Norsborg, Sweden). A total work capacity (watt) test was performed on a bicycle ergometer.

Paper II

The population based Gothenburg Osteoporosis and Obesity Determinants (GOOD) study was initiated with the aim to determine both environmental and genetic factors involved in the regulation of bone and fat mass. Study subjects in the entire GOOD study were randomly identified using national population registers, contacted by telephone, and asked to participate in this study. A total of 1068 men, 18.9 ± 0.6 years of age, from the greater Gothenburg area were included. To be included in the GOOD study, subjects had to be between 18 and 20 years of age and willing to participate in the study. There were no other exclusion criteria; 48.6% of the contacted study subject candidates agreed to participate and were included in this study. The GOOD cohort was found representative of the general young male population in Gothenburg (118).

In paper II, the 390 men that were sedentary at the time of inclusion were used for the extended analysis (Table 1).

Height and weight were measured using standardized equipment. A standardized questionnaire was used to collect information about calcium intake (dairy products) and smoking. Grip strength was assessed using a Jamar hydraulic hand dynamometer (5030J1, Jackson, MI, USA) with adjustable handgrip.

Paper III

The 498 subjects included in the study were randomly selected from the population-based MrOS Göteborg study including 1010 men 70 to 80 years of age (119) (Table 1). There were no differences between the sub-sample, with 498 subjects, and the complete MrOS Göteborg cohort in age, height, weight, present physical activity, calcium intake, and smoking habits, indicating that the sub-sample is representative of the complete MrOS Göteborg study. The MrOS Göteborg study is a part of a multi-centre study including elderly men in Sweden (n=3014), Hong Kong (n≈2000), and the United States (n≈6000). All subjects were randomly sampled from the Swedish national population register for Göteborg and invited to participate on a voluntary basis. Men who could not walk indoors without walking aid were excluded.

Height and weight were measured using standard equipment. A standardized self-reported questionnaire was used to collect information about amount of present physical activity (total daily walking distance), calcium intake, smoking habits, and the prevalence of diseases. Current medication was collected at interview. Grip strength was assessed using a Jamar hydraulic hand dynamometer (5030J1, Jackson, MI, USA) with adjustable handgrip.

Paper IV

The study subjects were initially enrolled in the population based GOOD study with the aim to determine both environmental and genetic factors involved in the regulation of bone mass (118). All study subjects in the original GOOD study were contacted by letter and telephone and invited to participate in this five-year follow-up study. A total of 829 men, 24.1±0.6 years of age, from the original population of 1068 subjects were included in the study. The original GOOD cohort was found representative of the general young male population in Gothenburg (118). To determine whether the cohort of the present study also was representative of the initial population, we compared the age, height, weight, and amount of present physical activity (all variables measured at the time of inclusion in the original GOOD study) of the included subjects (n=829) with the subjects that were not included (n=239) in the study (Table 1). There were no significant differences between the included and not included subjects in age, height, weight, or amount of present physical activity.

Height and weight were measured using standardized equipment. A standardized self-administered questionnaire was used to collect information about calcium intake (dairy products), alcohol intake and smoking.

Ethics

In the studied cohorts in paper I–IV, written and oral informed consent was obtained from all study participants. For adolescents in the cohort in paper I younger than 18 years of age, written informed consent was also obtained from their parents. The regional ethical review board at the University of Gothenburg approved all four studies.

Bone mass measurements

Measurement of bone mass, e.g. bone mineral density (BMD), bone geometry, and bone microarchitecture, is of central importance in the assessment of bone fragility. Bone mineral density, bone geometry, and bone microarchitecture are good estimates of mechanical strength of the bone and resistance against fracture (2, 31-33). For this purpose, a number of non-invasive methods have been developed. Dual energy X-ray absorptiometry (DXA) is currently the most widely used method to evaluate areal BMD (aBMD) in clinical practice, and the WHO criteria for the diagnosis of osteoporosis and osteopenia are based on BMD measurements with this technique.

Historically, the most commonly used method in a research setting has been DXA, and two different DXA techniques, peripheral and whole body respectively, were used in the cohort in paper I and III in this thesis. However, other non-invasive techniques, e.g. quantitative computed tomography (QCT) and magnetic resonance imaging (MRI), that allows an examination of bone tissue in more detail, e.g. volumetric bone mineral density (vBMD), bone geometry, and bone microarchitecture, have also been developed. Two different QCT techniques, peripheral quantitative computed tomography (pQCT) and high-resolution peripheral quantitative computed tomography (HR-pQCT) respectively were used in the cohorts in paper II and IV in this thesis.

Dual energy X-ray absorptiometry (DXA)

The underlying principle of the DXA technique is that different tissues absorb energy to different degrees. A dual energy spectrum is created from an X-ray source and by a filter. Sensors detect the amount of energy absorbed when each X-ray passes through the body. The use of two energies makes it possible to distinguish between soft tissues and bone, and allows bone mineral to be assessed independently of soft tissue.

A DXA measurement results in a two dimensional projection of the bone, produces results based upon a weighted average of combined trabecular and cortical bone where only changes in length and width are accounted for. Therefore, an aBMD (g/cm^2), corresponds to the amount of bone mineral per area unit and not the true amount of bone mineral per volume unit (vBMD, g/cm^3). Thus aBMD provides no information about the size and depth of the bone, which means that if a large and small bone have the same volumetric BMD the larger bone will falsely have higher aBMD (120). The two dimensional projection of the bone will neither reveal important information about bone structure, i.e. connectivity and number of trabecular bone, nor size and thickness of the cortical bone, both important determinants of bone strength (120). DXA measurements gives information on aBMD, bone mineral content (BMC) and bone area for individual bones as well as the whole body. The total body DXA scan, also measures body constitution parameters, i.e. fat and lean mass.

Paper I

Areal BMD (g/cm^2), BMC (g), and bone area (cm^2) of the calcaneus were measured using a dual energy X-ray absorptiometry (CalScan DEXA-T). CalScan uses the DXA technique with two mean photon energies (30 and 60 KeV). The effective radiation dose is 0.2 μSv per scan (121). The same device and software were used throughout the whole study.

Paper III

Areal BMD (g/cm^2), BMC (g), and bone area (cm^2) of the total body, total hip, femur trochanter, and lumbar spine (L1-L4) were assessed using the DXA Hologic QDR 4500/A-Delphi (Fig. 2). Areal BMD, BMC and bone area of the right arm were derived from the total body scan. The effective radiation dose is up to 4 μSv per scan dependent on measured bone site (122). The same device and software were used throughout the whole study.

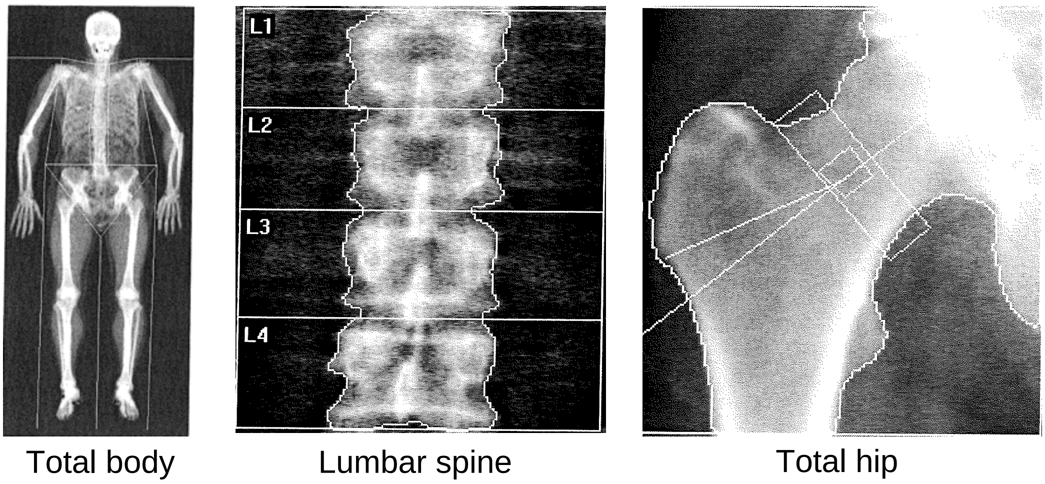

Figure 2*. Images of the total body, lumbar spine, and total hip measured with DXA (DXA Hologic QDR 4500/A-Delphi).*

Peripheral quantitative computed tomography (pQCT)

Peripheral quantitative computed tomography (pQCT) is a technique that allows a three-dimensional assessment of the bone, making it possible to measure true vBMD, bone dimensions, and even microarchitecture. This technique can also differentiate between cortical and trabecular bone, enabling these bone components to be studied separately.

The pQCT is a method that only can measure peripheral bones, and the technique is based on a rotating X-ray source that moves to fixed positions around the measured limb, typically an arm or leg. A computer processes multiple cross-sectional X-rays to reconstruct a volumetric model of the bone density distribution and produces an image that represents a section of the body part being measured. The radiation dose is similar to the dose produced by DXA, and is considered safe since radiation is restricted to the measured limb and very low to the central body (123). The analyzed bone mineral density is presented as mg/cm^3. Currently the pQCT technique is mainly used as a tool in research settings, because the WHO has not yet defined thresholds for diagnosing osteoporosis using pQCT measurements like it is done for DXA measures (124).

Paper II

A pQCT device (XCT-2000; Stratec Medizintechnik, Pforzheim, Germany) was used to scan the distal leg (tibia) and the distal arm (radius) of the non-dominant leg and arm, respectively. A 2-mm-thick single tomographic slice was scanned with a voxel size of 0.50 mm.

As the diaphyseal site primarily is composed of cortical bone (Fig. 3), the cortical vBMD (not including the bone marrow; mg/cm^3), cortical cross-sectional area (CSA, mm^2), endosteal and periosteal circumference (EC and PC, mm), and cortical thickness (mm) were measured using a scan through the diaphysis (at 25% of the bone length in the proximal direction of the distal end of the bone) of the radius and tibia. Whereas the metaphyseal site primarily is composed of trabecular bone (Fig. 3), trabecular vBMD (mg/cm^3) was measured using a scan through the metaphysis (at 4% of the bone length in the proximal direction of the distal end of the bone) of these bones. Tibia length was measured from the medial malleolus to the medial condyle of the tibia, and length of the forearm was defined as the distance from the olecranon to the ulna styloid process. The examination is easy and comfortable for the subject with a total procedure time of about 90 seconds per scan. The effective radiation dose is less than 3 μSv per scan (manufacturer specifications), and is restricted to the measured limb (123). The same device, software and operator were used throughout the whole study.

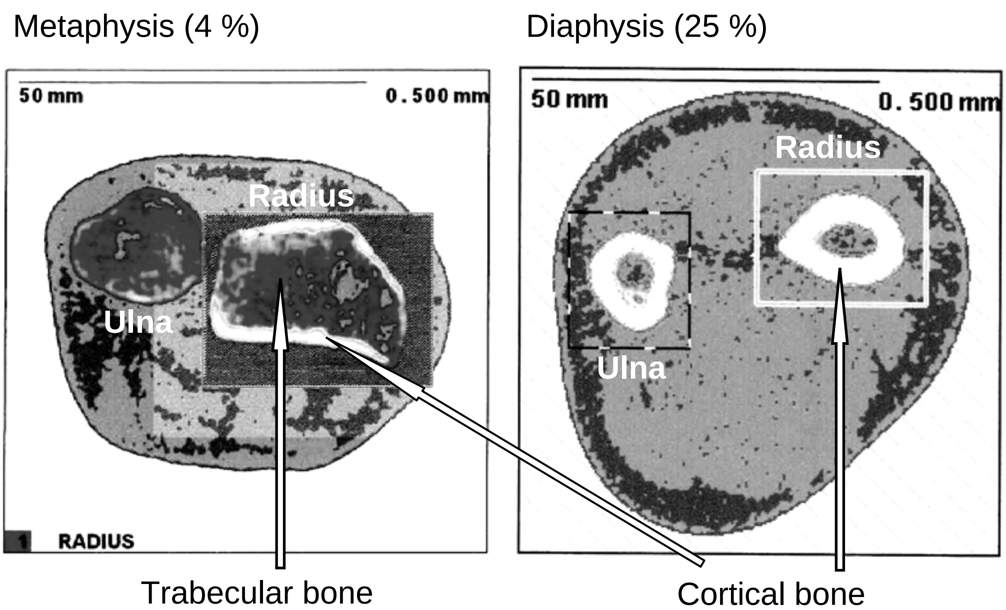

***Figure 3**. Images of a metaphyseal and diaphyseal transversal cross-section of the radius measured with pQCT (XCT-2000).*

Paper IV

A high-resolution 3D pQCT (HR-pQCT) device (XtremeCT, Scanco Medical AG, Switzerland) was used to scan the ultra distal tibia and the ultra distal radius of the non-dominant leg and arm, respectively. The right arm and leg of right-handed men was defined as their dominant side, while the left arm and leg of left-handed men was defined as their dominant side. Anatomically formed carbon fiber shells, especially designed for each type of limb (Scanco Medical AG, Switzerland), were used to immobilize the subjects arm or leg during the scan. The measurements of the volume of interest in the ultra distal tibia and radius, 1 cm in the proximal direction and the whole cross-section in transversal direction (Fig. 4), were carried out according to a standardized protocol previously described (125, 126). Briefly, a reference line was manually placed at the centre of the endplate of the distal tibia and distal radius. The first CT slice started 22.5 mm and 9.5 mm proximal to the reference line for the tibia and radius, respectively. One hundred ten parallel CT slices, with a nominal isotropic resolution (voxel size) of 82 µm, were obtained at each skeletal site, delivering a three-dimensional representation of approximately 9 mm section of both the tibia and radius in the proximal direction.

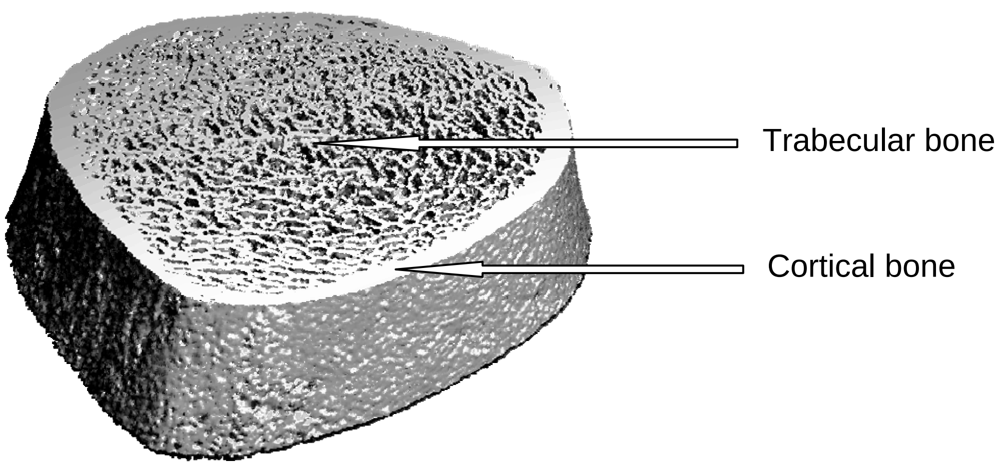

***Figure 4**. An image of a metaphyseal transversal cross-section of the tibia measured with HR- pQCT (XtremeCT, Scanco Medical AG, Switzerland).*

At each skeletal site, the entire volume of interest was automatically separated into a cortical and a trabecular region (Fig. 4). From this separation and by previously described methods to process the data (126), we obtained volumetric trabecular bone density (D.Trab, mg/cm^3), trabecular bone volume fraction (BV/TV, %), trabecular number (Tb.N, mm^{-1}), trabecular thickness (Tb.Th, μm), cortical cross-sectional area (Cort.CSA, mm^2), cortical thickness (Cort.Th, mm), cortical periosteal circumference (Cort.Pm, mm), volumetric cortical bone density (D.Cort, mg/cm^3), and total bone area (Tot.Area, mm^2). The examination is easy and comfortable for the investigated subject with a total procedure time of about three minutes per measurement. The effective radiation dose is less than 5 μSv per scan (manufacturer specifications), and is restricted to the measured limb (123). The same device, software, and operator were used throughout the whole study.

Due to artefacts caused by inadequate limb fixation, the quality of the measurements on the tibia and radius were assessed by a five graded scale, recommended by the manufacturer (Scanco Medical AG, Switzerland), where 1 had the highest quality, 2 to 3 acceptable quality (included in the analyses) and grade 4 to 5 had unacceptable quality (excluded from the analyses).

Assessment of physical activity habits

In paper I–IV, standardized questionnaires were used to collect information concerning patterns and type of physical activity in sports using a lifetime perspective. Self administrated questionnaires were used in paper I, II, and IV, while the information was collected at interview in paper III using a standardised questionnaire previously described (127). In addition, information about occupational physical load was also collected at interview in paper III (127). In paper IV, a standardized self-administered questionnaire, based on a validated physical activity questionnaire to measure the effect of mechanical strain on bone mass (128) with amendments, was used. Occupational or leisure manual labour was not considered in paper I, II, and IV.

In paper I–IV, type of physical activity was categorized according to a strain score, based on ground reaction forces of sport activity and classified according to a method previously described (129, 130). Activities involving jumping actions (e.g., gymnastics, handball, basketball) were given a strain score of 3, activities including explosive actions like turning and sprinting (e.g., soccer, tennis, ice hockey) were given a strain score of 2, while other weight-bearing activities (e.g., jogging, martial arts, strength training) were given a strain score of 1. Non-impact activities (e.g., swimming, bicycling, and sailing) were given a strain score of 0. If subjects in paper I and III participated in several types of sports, an average strain score was calculated, by the sum of all strain scores divided by number of sports.

In order to analyze the role of both type and amount or frequency of sport activity on bone parameters, we calculated an osteogenic index (OI) based upon a previously described method (131). The osteogenic index was used in paper I–III and constructed by multiplying time spent on sport activity with related sport activity strain score for each subject. In paper I and III, the osteogenic index was constructed by multiplying time or frequency of physical activity, respectively, with the average sport activity strain score for each subject. In paper II the osteogenic index was constructed by multiplying the amount of sport activity with the sport activity strain score for each type of sport activity and then summarizing all the products for all types of previous sport activity for each subject.

Statistics

All data was analyzed using the SPSS software version 15.0 for Windows. In paper I, II, and IV, differences in characteristics and bone parameters between subjects divided according to physical activity habits were calculated using analysis of variance (ANOVA) followed by least significant difference post hoc test for continuous variables. In paper III, differences in characteristics and bone parameters between the different physical activity groups were studied using an independent samples t-test. Comparisons of categorical variables were calculated using χ^2 test in paper I–IV. In paper I–III, bivariate correlations between various parameters of bone and physical activity were tested using Pearson's coefficient of correlation. In paper I–IV, the independent predictors of each bone parameter were tested using stepwise multiple linear regression analysis, including age, height, weight, calcium intake, smoking, and physical activity. The stepwise selection process criterion for entry into the model was a p-value ≤ 0.05, and the criterion for removal from the model was a p-value ≥ 0.10. Parameters that did not display a normal distribution were logarithmically transformed before entered into the regression model.

In paper I, II, and IV, the percentage of the variation (R^2), of each bone parameter, explained by different variables of physical activity, together with all covariates was calculated using the stepwise linear regression model. R^2 for each variable was calculated as the R^2 change of the entire model when adding each variable, until all variables were included in the regression model. In order to estimate the age of peak bone mass in paper I, quadratic regression analysis was performed, including age, squared age, height, weight, calcium intake, smoking, and history of physical activity. Age of peak bone mass, the maximum point of the curve where the slope of the tangent is equal to zero, was calculated by using the unstandardized β-values from the quadratic regression model.

RESULTS

Paper I

Physical activity during growth and calcaneal BMD

To investigate the association between physical activity during growth and calcaneal peak bone mass, we used a highly representative cohort of young Swedish men (18-years old) consisting of 2,384 subjects.

Results

- History of regular physical activity was associated with aBMD, BMC, and bone area at the calcaneus.
- Number of years of regular physical activity was found to be the strongest predictor and could explain 10.1% of the variation in calcaneal aBMD.
- Type together with duration of regular physical activity (OI) could explain 10.3% of the variation in calcaneal aBMD.
- Age was associated with aBMD at the calcaneus and our results indicated that peak bone mass was attained at the age of 18.4 years.
- Men who had retired from sport activity they participated in during growth had higher aBMD, BMC, and bone area at the calcaneus than always-inactive men, indicating lasting positive effects of physical activity despite of cessation.

In conclusion, we found that history of physical activity during childhood and adolescence was the strongest predictor of BMD at the calcaneus in a large and highly representative sample of young adult Swedish men.

Paper II

Sport activity during growth and cortical bone geometry

To investigate the association between previous physical activity during growth and cortical bone geometry in tibia and radius, we investigated 390 currently inactive young adult men (19-year old) from the GOOD cohort.

Results

- Young adult men previously engaged in sport activity had greater cortical cross-sectional area (CSA) and periosteal circumference (PC) of the tibia than always-inactive subjects. No differences were seen at the corresponding bone parameters of the radius.
- Amount of previous sport activity explained 7.3% of the total variation in cortical CSA of the tibia.
- Amount together with type of previous sport activity (OI) explained 7.9% of the total variation in cortical CSA of the tibia.
- Young adult men, who ceased their sport activity for up to 6.5 years previously, still had greater cortical CSA and PC of the tibia than always-inactive subjects.

In conclusion, we found that sport activity during childhood and adolescence was associated with increased cortical bone size in currently physically inactive Swedish young adult men, suggesting that sport activity during growth confers positive effects on bone geometry even though sport activity is ceased.

Paper III

Competitive sport activity early in life and areal bone mineral density

To investigate the association between physical activities early in life and areal bone mineral density in elderly men, we investigated 498 men (75-year old) from the MrOS cohort.

Results

- Elderly men who had participated in competitive sports during life had higher aBMD at the total body, hip, lumbar spine, and right arm and higher BMC at the total hip than men who had not participated in any competitive sport.
- Frequency of competitive sport activity early in life (between 10-35 years of age) was an independent predictor of aBMD at the total body, total hip, lumbar spine, and right arm and BMC at the total hip and total body in elderly men.
- Frequency together with type of competitive sports (OI) early in life predicted aBMD and BMC in the same way as frequency of competitive sports did alone.
- No correlations between frequency of recreational sport activity or occupational physical load for any period and present aBMD were found at any measured bone site.

In conclusion, our results demonstrated that physical activity in competitive sports with a high frequency early in life was associated with aBMD and BMC in 75-year-old Swedish men, indicating that increases in bone mass following physical activity are preserved longer than previously believed. These novel findings suggest that high frequency physical activity early in life could aid in preventing osteoporosis in elderly men.

Paper IV

Physical activity, trabecular microstructure and cortical bone at distal tibia

To investigate if present or previous physical activity were associated with trabecular microstructure and cortical bone geometry in weight-bearing bone, we investigated a cohort of 829 young adult men (24-year old).

Results

- Total amount of physical activity, duration of previous physical activity, and degree of mechanical loading in weight-bearing bone (tibia) due to type of physical activity during the past 12 months were associated with trabecular microstructure and cortical bone size.
- Men with the highest degree of mechanical loading had higher tibial trabecular bone volume fraction (13.9 %) and trabecular number (12.7 %) than men with the lowest degree of mechanical loading due to physical activity.
- Men in the group with the longest duration of physical activity had higher cortical cross-sectional area (16.1 %) than sedentary men at the tibia.
- Degree of mechanical loading due to physical activity independently predicted tibial trabecular bone volume fraction and trabecular number.
- Duration of previous physical activity independently predicted cortical cross-sectional area at the tibia.

In conclusion, we demonstrated that the degree of mechanical loading due to type of present physical activity was predominantly associated with trabecular microstructure, while duration of previous physical activity was mainly related to parameters reflecting cortical bone size in weight-bearing bone.

DISCUSSION

Given the evidence from numerous studies, there is no doubt that weight-bearing mechanical loading applied dynamically by physical activity has positive effects on bone enhancement (78-86, 88-90). The overall aim of this thesis was to gain a better understanding of the role of both physical activity and inactivity on bone density, bone geometry, and trabecular microarchitecture in men. Although several previous controlled intervention trials have found that exercise has positive effects on bone health during growth in boys, the long term effects are still debated (96, 117). Some studies have reported that the exercise-induced benefits on aBMD are lost after retirement from training (108, 109). In contrast, several other studies have shown that the positive effects previous training have on bone will remain when the level of activity is decreased, and even after complete cessation of exercise (6, 110-116). Our findings in paper I, II, and III support the findings of these latter studies. The limitation of using DXA, as in the majority of the studies assessing the bone phenotype can be one reason for the lack of consensus in these previous findings. However, in two of the studies, reporting remaining effects of physical activity, athletes had greater bone size after retirement (115, 116).

In paper I, we investigated the association between sport activity during growth and calcaneal BMD in young adult men retired from exercise compared with always inactive men. We found that calcaneal BMD was higher in men who had ceased to be active than men who had always been inactive. Since the calcaneus is a weight-bearing bone directly exposed to mechanical loading, the calcaneus is an highly relevant and interesting bone site for evaluation of the effect of physical activity on bone (132). In paper I, we also found that men who ceased to be active had greater calcaneal body size-adjusted bone area than the always-inactive subjects. As calcaneal body size-adjusted bone area is an estimate of bone geometry, we hypothesize that our findings indicate that exercise during growth can contribute to bone enlargement, and that the positive effects on bone geometry is preserved into adulthood even if the training has been ceased.

In paper II, we investigated the association between sport activity during growth and cortical bone geometry of the tibia in young adult men retired from exercise compared with always-inactive subjects. Some previous studies investigating bone geometry have reported that physical activity during growth has a positive effect on cortical bone size (75, 101, 133). However, it is not known whether any positive effects of sport activity during growth on cortical bone geometry persist until adulthood in men. In paper II, we found that young adult men retired from the sport activity they participated in during growth had greater cortical cross-sectional area, cortical thickness, and cortical periosteal circumference of the tibia than subjects who had never exercised. Our findings indicate that sport activity during growth confers positive effects on bone geometry even though the activity is ceased.

In paper III, we investigated the association between competitive physical activity early in life and aBMD in elderly men retired from training compared with subjects that never had been active in competitive sports. If the positive effects will not maintain into late adulthood, when fractures occur, these exercise induced skeletal benefits could be questioned. A retrospective study suggests that men who were elite soccer players up to 25 years prior to examination had higher BMD than controls (134). However, the corresponding differences could not be seen for those who trained at this level 35 years or more prior to the examination (134). In paper III, we reported that men who had participated in competitive sports with a high frequency (≥3 times/week) during the period 10-35 years of age had higher aBMD at the total body, hip, and lumbar spine at the age of 75 years than men of the same age who never had participated in any competitive sports. Frequency of competitive sports early in life (10-35 years of age) was found to be an independent predictor of aBMD at the total body, hip, and lumbar spine in 75-year old men after adjusting for age, height, weight, calcium intake, smoking habits, present physical activity, recreational sport activity as well as occupational physical load in a life time perspective, as well as competitive sport activity after the age of 35 years. These novel findings indicate that increases in bone mass following physical activity could be preserved up to 40 years after retirement from training. When we compared BMD between the extreme groups of competitive sports early in life (≥3 times/week) and those who never had participated in any competitive sports the BMD differences were substantial. The differences ranged from 4.2%, at the total body, to 8.7%, at the femur trochanter. These differences correspond to nearly one half SD in BMD. Considering that the risk of hip fracture in men is increased three-fold per SD decrease in femoral neck BMD (135), it is possible that these differences in BMD could, at least partly, affect fracture risk.

When BMD is measured by DXA as in paper III, a large bone will show a falsely high BMD. Results reported by us in paper I and II together with previous studies have showed that physical activity during growth is associated with an altered cortical bone geometry, especially attributed to bone size (75, 85, 101). Thus, if the elderly men who were active in competitive sports during growth achieved a greater bone size, it is possible that this alteration is reflected by a higher aBMD, as measured with DXA in paper III.

Since it is well known that sport activity types with high strain give the most favorable bone acquisition in weight-bearing bones (78-83), we calculated osteogenic index for sport activity in paper I, II, and III. The osteogenic index was based on the amount or frequency as well as type of previous sport activity, where the role of ground reaction force was taken into account. When we added type of physical activity, by using this osteogenic index, in the regression analyses the explanatory role of physical activity in the model was somewhat increased in the associations with bone parameters. Thus, our results in paper I, II and III are concordant with previous findings supporting the role of high strain sport activity in bone acquisition.

Both cortical bone size and volumetric bone density (vBMD) are important determinants of bone strength and resistance against fracture (31, 32). As the resistance of bone to bending and torsion forces is related exponentially to its diameter, even a small difference in the outer circumference could have a substantial contribution to its strength and resistance to fracture (32). Previous studies on both mice (136) and growing boys (101) have shown that bone loading exercise resulted in increased periosteal circumference. With these reported findings in perspective together with our results in paper II, we speculate that the maintained benefits in terms of greater bone size of previous training when the exercise is ceased probably derive from periosteal apposition. As periosteal augmentation confers considerable benefits in terms of greater bone strength (32) this reveals a possibility that both type and amount of physical activity during growth could be important contributors to increase bone mass and also perhaps reduce the risk of fracture later in life. In line with a previous study conducted in female tennis players, where the dominant arm had higher trabecular vBMD compared to the non-dominant (137), we also found a positive association between previous sport activity and trabecular vBMD in paper II. Furthermore, we reported even stronger association between previous sport activity and cortical bone size in paper II. These findings are in agreement with previously reported increase in cortical bone size of the playing arm in male tennis players, compared to the non-playing arm (115).

Although we in paper II could show an independent association between previous sport activity and cortical bone size, e.g. cortical cross-sectional area and periosteal circumference, it should be taken into consideration if these findings could have any clinical relevance concerning risk of fracture later in life. In postmenopausal women, each SD decrease in cortical cross-sectional area has been associated with 3.6 times increase risk of radius fracture (138). If these results could be translated to young adult men as in paper II, where we found a difference in tibia cortical cross-sectional area between previously physically active and always inactive subjects equal to approximately 0.5 SD, previous physical activity could result in nearly halved risk of future fracture. Based on additional findings in paper II, it should be pointed out that continuing physical activity is probably needed to preserve the achieved or even increase cortical bone size into adulthood. We found that those men who had continued to be active in sports until time of inclusion, had even larger cortical bone size than previously active subjects.

Peak bone mass is reached somewhere between the end of the second decade and the end of the third decade in life dependent on studied bone site (43-49). In paper I, our results indicated, supported by previous studies, that peak bone mass at some bone sites can be obtained as early as between 18 and 19 years of age in men (43, 118, 139). We also found that physical activity seemed to be the strongest predictor of calcaneal peak bone mass. As several studies have indicated, peak bone mass could be an important determinant of osteoporosis later in life (3-5). Therefore, we think it is of great importance to encourage physical activity during growth with the aim to maximize the opportunity to attain a strong skeleton and hopefully prevent osteoporosis later in life.

In paper IV, we investigated the relationship between trabecular microstructure in weight-bearing bone and physical activity habits in young adult men with focus on present sport activity type and amount. To our knowledge, this is the first study examining the association between exercise and trabecular microstructure in men. A previous report, conducting computer generated models using 3D reconstructions of trabecular bone architecture, reported that loss of trabeculae is of greater importance for the bone strength rather than reduced trabecular thickness (61). In paper IV, we demonstrated a positive association between present exercise with high degree of mechanical load and augmented tibial trabecular vBMD, due to increased trabecular number but not altered trabecular thickness, indicating that high-load physical activity results in increased bone strength due to enhanced trabecular bone microstructure. Furthermore, our results indicated that degree of mechanical loading due to type of present sport activity was more important than amount of present sport activity in the enhancement of both trabecular microstructure and cortical bone dimensions.

There are some limitations associated with the studies in paper I–IV. In the cross-sectional design, there is always a risk of selection bias in the inclusion process that will reduce the possibility of generalization of the results. However, in paper I we collected data from a large (n=2,384) randomized selected sample from a cohort covering 95% of the male population, 18-20 years of age, in the western part of Sweden. In addition, a very large proportion (95%) of the subjects that were asked to participate was included in the study. We believe this makes the studied sample of young adult men a highly representative cohort of the total population of young Swedish men. As the results in paper I in many ways point in the same direction as in paper II, III, and IV, we also believe that there is potential of possible generalization in our results. The clear association between sport activity during growth and BMD and bone size in paper I, II, and IV, and the positive effect on bone size seems to remain even when the sport activity is ceased shown in paper I, II, and III. However, results from the studies in paper I–IV derive from investigations on samples of men with narrow age ranges, and may not therefore be applicable to other age groups.

Another limitation of the cross-sectional design is that it does not allow direct cause-effect relationships to be established between the studied parameters. It is possible that men with genetically larger and stronger bones could be more likely to be more successful in and participate to a higher extent in strenuous physical activity sports during growth. However, we could not find any differences in body size parameters (height or weight) between subjects in the different studied groups of athletes and non-athletes in paper I–IV.

Lifetime physical activity participation was assessed using retrospective questionnaires, which could have limited the ability of the subjects to recall past activity and cause bias and misclassification. However, several studies have reported that people can recall activity patterns of up to 10 years ago with high reliability and that recall of more vigorous activity is more accurate than recall of less intensive activities (88, 140, 141). Thus, the use of self-reporting questionnaires in paper I, II, and IV possibly allowed the collection of accurate information about sport activity habits during growth. Furthermore, in paper III, where we studied elderly men, we optimized the possibility for subjects to make a correct recall of their previous habits of physical activity even during growth, by collecting all physical activity data by interview.

Conclusions

In conclusion, the findings in this thesis indicate that physical activity during growth plays an important role in the optimization of peak bone mass and bone geometry, with lasting benefits even though physical activity is ceased. With these reported findings in perspective, we suggest that physical activity during growth confers a lasting positive effect on bone density and geometry and can contribute in the prevention of bone loss in men. We also demonstrated that the degree of mechanical loading due to type of present physical activity was predominantly associated with trabecular microstructure, while duration of previous physical activity was mainly associated with parameters reflecting cortical bone size in weight-bearing bone.

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