

Saija Kontulainen

Training, Detraining and Bone

Effect of Exercise on Bone Mass and Structure with  
Special Reference to Maintenance of the Exercise-  
induced Bone Gain

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UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2002

# **Training, Detraining and Bone**

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## ABSTRACT

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Finnish summary

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The objectives of this thesis were to investigate the effects of long-term mechanical loading on mass, size and mechanical strength of bone in male and female racquet sports players and to evaluate the maintenance of exercise-induced bone gain in these players during the following years of reduced training. In addition, bone maintenance was assessed after jumping exercise interventions in pubertal girls and premenopausal women. Altogether 223 subjects were involved in the study serie. The cross-sectional comparisons of bone mass, structure and strength between playing and nonplaying arm of racquet sports players showed that playing had increased bone size but not volumetric density of cortical bone. The loaded bone shaft seemed to have grown periosteally leading to 11-34% greater estimated bone strength in the loaded arm compared to its counterpart. In female players, this exercise-induced benefit in bone strength was more than two times greater if starting age of the activity had been before the onset of puberty. Prospective 4- and 5-year follow-up studies of male and female racquet sports players and their controls revealed that despite reduced training the exercise-induced bone gain was well maintained in all groups of players regardless of the starting age of activity (either in growing years or in adulthood) and different amount of exercise-induced bone gain. Changes in training were weakly related to the changes in the side-to-side BMC difference even among players who had completely stopped training a minimum one year before the follow-up. As regards, the maintenance of the effects of jumping interventions on bone and physical performance were evaluated in perimenarcheal girls and in premenopausal females. Girls' follow-up showed that although the greatest proportion of bone mineral accrual was attributable to growth, an additional bone gain achieved by jumping training was maintained at the lumbar spine at least a year after the end of the training. In premenopausal women, the significant bone gain that was obtained by 18-month high-impact exercise was well maintained three and half years after the end of the intervention, while the exercise-induced improvements in the neuromuscular performance had returned to the baseline level. All these findings emphasise long-term benefits of exercise on bone. Therefore, exercise can be recommended for preventing osteoporosis and related fractures.

KEY WORDS: bone gain, bone mineral, bone strength, pQCT, DXA, exercise, tennis, training, detraining, osteoporosis

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New information increases our knowledge. We learn when we understand its meaning. But to use it right we need wisdom.

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Saija Kontulainen

## ABBREVIATIONS

ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
aBMD	Areal bone mineral density, g/cm <sup>2</sup>
BMD	Bone mineral density, mg/cm <sup>3</sup>
BMC	Bone mineral content, g or mg
BMI	Body mass index, kg/m <sup>2</sup>
BMU	Bone multicellular unit
BSI, BSIt	Bone strength index, against torsion, mm <sup>3</sup>
BSIc	Bone strength index, against compression, g <sup>2</sup> /cm <sup>4</sup>
CavA	Cross-sectional area of the marrow cavity, mm <sup>2</sup>
CI	Confidence interval
CT	Computed tomography
CoA	Cross-sectional area of the cortical bone, mm <sup>2</sup>
CoD	Volumetric density of the cortical bone, mg/cm <sup>3</sup>
CSMI	Cross-sectional moment of inertia, cm <sup>4</sup>
CV	Coefficient of variation, %
CWT	Cortical wall thickness, mm
DXA	Dual energy x-ray absorptiometry
FN	Femoral neck
GLM	General linear model
LS	Lumbar spine
MRI	Magnetic resonance imaging
PBM	Peak bone mass
pQCT	Peripheral quantitative computed tomography
ROI	Region of interest
SD	Standard deviation
TotA	Total cross-sectional area of bone, mm <sup>2</sup>
TrD	Volumetric density of the trabecular bone, mg/cm <sup>3</sup>
Z	Section modulus, mm <sup>3</sup>

## LIST OF ORIGINAL PUBLICATIONS

- I Haapasalo H, Kontulainen S, Sievänen H, Kannus P, Järvinen M, Vuori I 2000. Exercise-induced bone gain is due to enlargement in bone size without a change in volumetric bone density: a peripheral quantitative computed tomography study of the upper arms of male tennis players. *Bone* 27:351-7.
- II Kontulainen S, Sievänen H, Kannus P, Pasanen M, Vuori I 2002. The effect of long-term exercise on mass, size, and estimated strength of radius and humerus of female racquet-sports players. A peripheral quantitative computed tomography comparison between young and old starters and controls. *J Bone Miner Res*. In press.
- III Kontulainen S, Kannus P, Haapasalo H, Heinonen A, Sievänen H, Oja P, Vuori I 1999. Changes in bone mineral content with decreased training in competitive young adult tennis players and controls: a prospective 4-yr follow-up. *Med Sci Sports Exerc* 31:646-52.
- IV Kontulainen S, Kannus P, Haapasalo H, Sievänen H, Pasanen M, Heinonen A, Oja P, Vuori I 2001. Good maintenance of exercise-induced bone gain with decreased training of female tennis and squash players: a prospective 5-year follow-up study of young and old starters and controls. *J Bone Miner Res* 16:195-201.
- V Kontulainen S, Kannus P, Pasanen M, Sievänen H, Heinonen A, Oja P, Vuori I 2002. Does previous participation in high-impact training result in residual bone gain in growing girls? One year follow-up of a 9-month jumping intervention. *Int J Sports Med*. In press.
- VI Kontulainen S, Heinonen A, Kannus P, Sievänen H, Pasanen M, Vuori I 2002. Good maintenance of high-impact activity-induced bone gain in premenopausal women. A 5-year follow-up of a randomized controlled trial. Submitted.

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ABSTRACT

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# 1 INTRODUCTION

Term osteoporosis was coined in French in the early 1820s as a mere description of a pathological state of the bone, and it made its way into the English medical vocabulary not until the twentieth century (Schapira & Schapira 1992). Over the years of its evolution, the definition of osteoporosis has constantly reflected the state of knowledge on the phenomenon itself and continuously sought to maintain a difficult balance between physiological and clinical criteria (Schapira & Schapira 1992). In 1990 Consensus Conference defined osteoporosis as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration with a consequent increase in bone fragility and susceptibility to fractures, thus implying the clinically most important aspect of osteoporosis – the risk of fracture. (Consensus Development Conference 1991)

Osteoporotic fracture occurs as a result of a low- or moderate-energy trauma, most often due to a fall of an elderly person. About two thirds of fall-induced injuries of older adults are bone fractures, hip fracture being the most common, most devastating, and most expensive for the health care systems (Kannus 1999). Several preventive actions have been shown to reduce the risk of osteoporotic fractures, including those that enhance bone mass and reduce the risk or consequences of falls (NIH Consensus Development Panel 2001). Regular exercise is probably the only method that may prevent both osteoporosis and falls (Kannus 1999). The greatest influence of exercise or mechanical loading on bone mass accrual seems to be at the time of rapid skeletal growth (Kannus et al. 1995, Haapasalo et al. 1998, Bailey et al. 1999, Khan et al. 2000), and thus, physical activity is important for the optimization of peak bone mass. In both pre- and postmenopausal women, resistance and high-impact activity training programs have shown to moderately reverse the age-related bone loss to mild-to-moderate bone gain, or, at least prevent further bone loss (Nelson et al. 1994, Lohman et al. 1995, Heinonen et al. 1996, Wallace and Cummings 2000, Wolff et al. 1999, Kelley et al. 2001, Vuori 2001). Exercise-induced enhancement in reaction time, balance, muscle strength, and coordination may also reduce the risk of falls in older persons (Campbell et al.

1997, Joakimsen et al. 1997, Heinonen et al. 1996, Robertson et al. 2001a, 2001b, Carter et al. 2001). Thus, combining the measurement of both neuromuscular function and bone strength would be the most accurate approach to assess an individual's intrinsic risk for osteoporotic fracture (Cummings and Nevitt 1989).

To evaluate bone strength accurately, the relationship between material and structural properties of bone should be assessed (Martin 1991, Einhorn 1996, Currey 2001). Currently, in both research and clinical practice, the most commonly used method to evaluate bone strength is dual energy x-ray absorptiometry (DXA), particularly DXA-derived areal bone mineral density (aBMD,  $\text{g}/\text{cm}^2$ ) (Marshall et al. 1996, Genant et al. 1996, Genant 1998). However, as aBMD represents a lumped measure of bone size and volumetric density, it is complicated to interpret (Sievänen 2000a). It is also subject to considerable patient-specific inaccuracies (Bolotin et al. 2001), and can thus, seriously mislead the diagnostic or prognostic interpretations of bone fragility (Bolotin and Sievänen 2001). In addition, the assessment of structural changes, redistribution of bone material, and compartments of trabecular and cortical bone (factors that are related to bone integrity and that may change due to mechanical loading or any other treatment), can be underestimated or even missed if depicted by planar densitometry (Kimmel 1993, Järvinen et al. 1998, Adami et al. 1999, Sievänen 2000a, Forwood 2001). However, in most cases, DXA is the only method available. Also, the operational guideline to diagnose osteoporosis by the World Health Organisation (WHO) is based on aBMD as the outcome (Kanis et al. 1994), whereas the "microarchitectural deterioration" in the definition has not achieved clinical application (Seeman 1997). Although decreased aBMD is associated with increased risk of fracture at the populational level it cannot identify those individuals who will eventually fracture (Marshall et al. 1996).

Thus, the relevance of aBMD as a surrogate for bone strength and as reliable assessor of bone treatment at the individual level has been recently challenged and the need for more sophisticated noninvasive methods to characterize bone accurately has been clearly brought up (Beck 1996, Järvinen et al. 1999, Faulkner 2000, Currey 2001, Bolotin and Sievänen 2001). While the development and acceptance of proper three-dimensional, imaging techniques is decisive to enable the accurate, noninvasive evaluation of bone integrity, the advancing state of knowledge should not lead only to a refined definition of osteoporosis. A comprehensive understanding of how, and to what extent, bone fragility can be influenced is closely linked to understanding the meaning of the prevention of falling –the main reason behind osteoporotic fracture. Prevention of the multifactorial problem like osteoporotic fractures requires prudent solutions in every aspect of its elements.

Although mechanical loading can increase bone mineral mass and aBMD considerably, especially during skeletal growth, little is known about the structural changes related to this additional bone mass. In addition, it is not known whether the possible alterations in bone cross-sectional geometry,

cortical and trabecular compartments, and bone size and strength depend on the age when bone is subjected to mechanical loading. Furthermore, there is contradictory evidence in the literature regarding the maintenance of exercise-induced bone mass after cessation of training. Retrospective cross-sectional studies on former athletes and their controls have given preliminary evidence that at least some residual benefits appear to be maintained into adulthood (Karlsson et al. 1995 and 1996, Lindholm et al. 1995, Kirchner et al. 1996, Khan et al. 1996, 1998, Bass et al. 1998, Karlsson et al. 2000, Magnusson et al. 2001). In contrast, some other human studies (Dalsky et al. 1988, Winters et al. 2000, Vuori et al. 1994) have shown that even a short detraining period reduces the exercise-induced bone gain to the pretraining values. This suggests that long-term benefits can only be retained with continuing exercise. While the response of bone to exercise seems to depend on the starting age of physical activity (Kannus et al. 1995), the response to reduced training and detraining may vary between the growing and mature skeleton. Despite the number of studies assessing the effect of exercise on bone, there are few follow-up studies that evaluate the maintenance of exercise-induced bone gain. Notably, there are no human studies that assessed the effect of starting age of an activity on the maintenance of exercise-induced bone gain.

Thus, the purpose of this thesis was to assess the effects of long-term mechanical loading and the starting age of activity on mass, size and estimated mechanical strength of bone in female and male racquet sport players. In addition, the aim was to evaluate the maintenance of exercise-induced bone gain in retired racquet sports players (who had started their training either during the growing years or in adulthood), as well as after the end of the exercise intervention in pubertal girls and premenopausal women. This work is a continuation to the earlier theses of the Bone Research Group of the UKK Institute (Heinonen 1997, Parkkari 1997, Haapasalo 1998, Järvinen 1999, Uusi-Rasi 1999, Leppälä 2000, and Palvanen 2001).



## **2 REVIEW OF THE LITERATURE**

### **2.1 Bone biology**

Bone is a vital connective tissue that has evolved to reflect a balance between its primary functions, i.e., provision of mechanical integrity for efficient locomotion together with the muscular system, protection of vulnerable inner organs, and involvement in the metabolic pathways associated with mineral homeostasis including serving as a mineral reservoir. In addition, bone is the primary site of hematopoiesis, and, thus, has a role in the immune system.

#### **2.1.1 Modeling and remodeling**

To maintain its functions bone tissue is constantly turned over by processes termed modeling and remodeling (Einhorn 1996, Parfitt 1996). In general, modeling refers to alterations in the shape of bone, whereas remodeling refers to turnover of bone that does not alter its shape. However, these two processes occur often simultaneously and the distinctions between them may not be readily apparent (Buckwalter et al. 1995).

Bone formation begins in utero and continues throughout adolescence until skeletal maturity (Einhorn 1996). Bone formation within cartilage (endochondral ossification) enables longitudinal skeletal growth, and enlarged width is a result of modeling within the organic matrix membrane (intramembranous ossification) and deposition of new bone on the existing surface (appositional ossification) (Buckwalter et al. 1995, Einhorn 1996). Following skeletal maturity, remodeling continues throughout life in order to maintain an adequate structure within a safety margin of normal mechanical demands. This is balanced by the cost of excessive bone mass on mobility (Turner 1991, Einhorn 1996). Remodeling also provides a mechanism to repair the damage created in bone by repetitive cycles of mechanical loading, and it enables the alteration of the essential minerals by increasing or decreasing their concentration in serum (Burr 2002).

The remodeling process is carried out by temporary anatomic structures known as basic multicellular units (BMUs), which excavate and replace tunnels in through cortical bone or the surfaces of cancellous bone. Each BMU includes two teams of executive cells (osteoclasts and osteoblasts) supported by blood vessels, nerves, and loose connective tissue (Parfitt 1996).

Bone remodeling occurs on periosteal, endosteal, Haversian canal and trabecular surfaces and each sequence follows a scheme of quiescence, activation, resorption, reversal, and formation (Parfitt 1984). The rate of cortical bone (re-)modeling, which can be 50% per year in the midshaft of femur during the first two years of life, declines to a rate of 2 to 5% per year in elderly people. In an adult, the remodeling rates in trabecular bone are, proportional to skeletal mass, approximately 5 to 6 times higher than rates in cortical bone. On average 5% of intracortical and 20% of trabecular bone surfaces are active with respect to bone remodeling (Parfit 1996).

### **2.1.2 Form follows function**

Bone has been defined as an organ of optimum structural design to serve its functions (Einhorn 1996). A whole bone's mechanical integrity depends mostly on the size, cross-sectional geometry, mass distribution, and internal architecture, whereas material properties vary less, and seem thus less important (Currey 1984). Although both cortical and trabecular bone have the same material properties, the difference in mineral distribution and microarchitecture within and between the texture of these two compartments, explains the differences in the mechanical properties of specific bones and parts of bones (Buckwalter et al. 1995). In general, biomechanical properties can be material or structural (Einhorn 1992, Turner and Burr 1993).

Inorganic matrix (mineral mass) mainly determines bone's rigidity as a material whereas the organic component of the tissue (collagen fibers and fibrils) is responsible for the elasticity of the material, allowing the transient deformation of the bone under the applied loads. After the external load is removed, bone will return to its original shape unless the applied loads exceed the yield point. Without sufficient elastic properties bone would be brittle like chalk (Currey 1984, Martin and Burr 1989) (Figure 1).

Mechanical properties of whole bone depend on the orientation of the applied forces; i.e., bone behaves anisotropically. Generally speaking, bone best withstands loads that are applied in the direction of customary loading. The form of human long bones, as thick-walled tubes and a dense cortical bone diaphysis, provide adequate stiffness against torsion and bending with the minimal mass required (Turner 1991). The longitudinal orientation of the osteons explain, in part, why diaphyseal cortical bone is strong in both tension and compression when it is loaded parallel rather than perpendicular to its long axis. In the metaphyses and epiphyses, the wide bone ends filled with trabecular bone broaden the bone end to form an articular surface. They also help cope with axial compression and spread out the applied load across the synovial cartilage (Buckwalter et al. 1995). Similarly, in short and flat bones, the

thin cortices are supported by trabecular bone inside. This structural form resists compression and impacts better than would cortical bone alone by allowing deformation to occur. The arrangement of trabeculae in positions of maximum stresses is such that the greatest strength is secured with a minimum of material (Currey 1984).

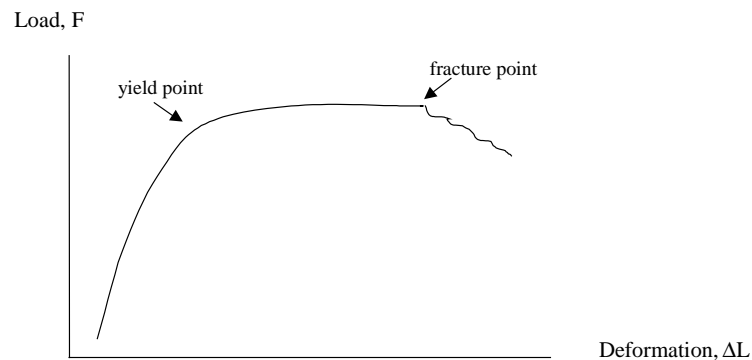


FIGURE 1 Load-deformation curve of bone. When a load is applied to bone, the bone deforms and an internal resistance (stress) is applied over the entire loaded section. Strain, in turn, describes the deformation of bone while subjected to an applied force, i.e., it is the ratio of the change in length to the original length of bone.

Although applied force can be directed to bone from any angle producing any set of complex stress patterns, all stresses can be resolved into three types: *tension*, *compression*, and *shear* (Figure 2). These basic stress types can result in a variety of complex loading configurations and may lead to different fracture patterns. Tensile force can produce a failure in bone when a tendon or ligament inserted into bone undergoes loading and, instead of tearing, it detaches itself from the bone by pulling a piece of bone off with it. These kind of avulsion fractures occur especially in children and adolescent since before the growth plates are closed the structure of bone is relatively frail (Jozsa and Kannus 1997). The common vertebral fracture sustained in osteoporotic patients is an example of the failure of bone as a result of compressive loading configuration. *Bending* results in a combination of tensile and compressive stresses, and *torsion* produces shear stresses along the entire length of bone and can result in a spiral fracture (Figure 2) (Einhorn 1992, Currey 1984, Martin 1991). Apart from the basic types of stress, it should be noted that bones seem to be poorly armed against the fall-induced sudden impact of loading. Most importantly, a typical hip fracture is the result of a fall and a subsequent direct impact on the greater trochanter of the proximal femur (Hayes et al. 1993, Parkkari et al. 1999).

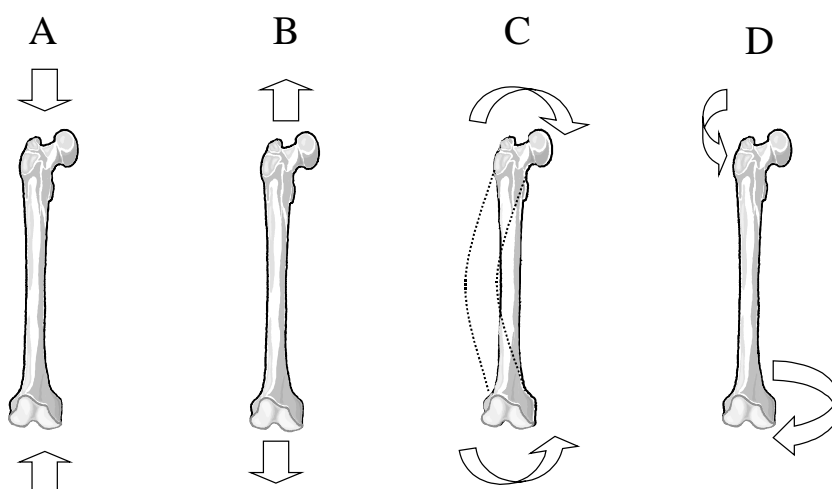
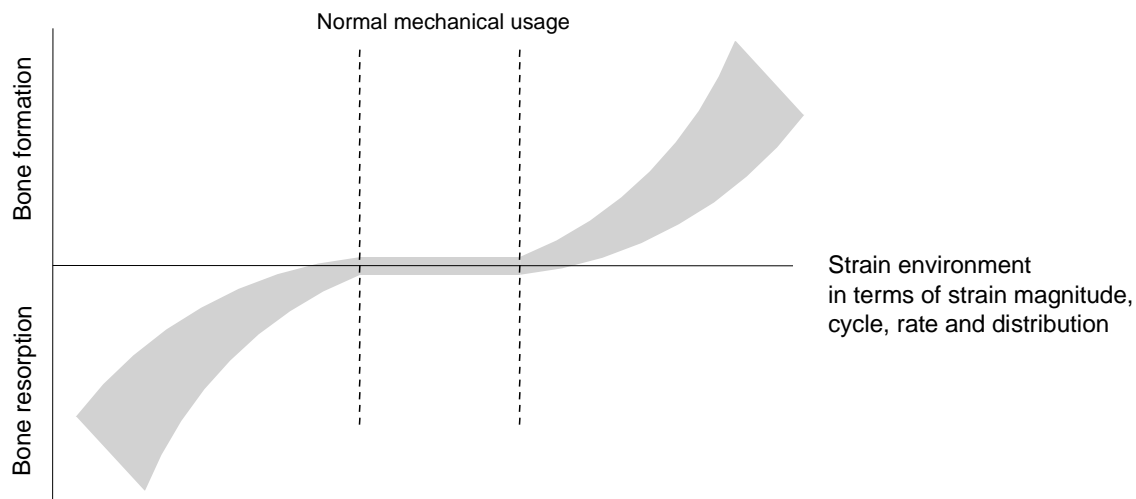


FIGURE 2 The principal types of loading experienced by bone in nature. Forces are expressed as arrows. Figure A represents compression, B tension, C bending (tension mainly on the convex side and compression on the concave side), and D torque (shear along the entire length of bone).

Achieving and maintaining mechanically appropriate bone mass and structure by loading is better understood at the bone tissue level than at cellular or subcellular levels (Rubin and McLeod 1996). The skeleton's ability to adapt to the functional demands was recognized a century ago, and has been since referred to as Wolff's law (Wolff 1892). The basic premise of this law is that an individual's level of activity tunes the mass and morphology of the skeleton such that it is sufficient to withstand functional loads but not so much as to make transportation a metabolic liability. At the tissue level this can be obtained by adjusting bone characteristics (mass, size, shape, cortical thickness, and trabecular architecture) in a direction that tends to keep the internal strains within a physiologically reasonable level. Modeling improves geometric properties by adding material where customary deformation is greatest (Kimmel 1993). Adding new bone on the periosteal surface and resorbing bone on the endocortical site increases section modulus and hereby diminishes the relative deformation of the predisposed load. Endocortical strains have been estimated to be clearly less than those at the periosteum, and are thus explained to be insufficient to initiate a bone formation response (Carter et al. 1996, Hsieh et al. 2001). However, even a lower threshold at the endocortex may be adequate to maintain bone mass and structure, and important to prevent cortical thinning during aging (Mosekilde 1993, Horikoshi et al. 1999). At the distal part of the lower extremities, where locomotion and body weight-induced strains are higher, the remodeling threshold could also be higher compared with proximal parts of these bones (Carter et al. 1996, Hsieh et al. 2001) (Figure 3).



**FIGURE 3** A scheme for bone response to mechanical loading. Adapted from Frost's "mechanostat" theory that describes bone's biologic mechanisms to adapt to its mechanical usage (Frost 1987). Mechanical usage effects on modeling drifts and bone multicellular unit-based remodeling affect bone mass and structure. Characteristics of strain within normal mechanical usage conserves existing bone whereas decreased mechanical usage will increase removal of bone next to marrow by remodeling while return to vigorous usage can increase bone mass by modeling. Other factors, such as nutrition, age, past loading, hormones and drugs, may modify the feedback control system by raising or lowering the mechanostat thresholds (Adapted from Frost 1987 and Carter et al. 1996).

Through the past decades, a number of specific components have been proposed as the dominant stimulus for "mechanotransduction" i.e. transformation of mechanical stimuli into biochemical signals for bone formation. Besides the different characteristics of strain (magnitude, cycles, rate, and distribution), these include prostaglandin release, shear-induced fluid flow, electric potentials, piezoelectric currents, microdamage and hormonally mediated mechanisms (Martin and Burr 1989, Chilibeck et al. 1995, Rubin and McLeod 1996). Evidence from experimental studies suggest that cyclic loading can move strain-mediated fluid-flow through the canalicular channels, and that shear stresses generated on bone cells seem to be proportional to the rate of loading (Burr et al. 2002). Deformation (and fatigue damage) experienced by the whole bone due to mechanical loading may also form an amplified strain. The sensor for these signals is a likely the lining cell-osteocyte complex (Kimmel 1993, Cowin and Weinbaum 1998, Martin 2000). Bone modeling and remodeling systems may then act as effectors and adjust strength and stiffness by changing mass and geometric properties of bone (Kimmel 1993).

### 2.1.3 Noninvasive assessment of bone fragility

Bone fragility is influenced by bone size, shape, structure, architecture, and quantity and quality of the tissue (Currey 1984, 2001, Einhorn 1992, Turner 2002). Biomechanical parameters, like ultimate breaking force or displacement (brittleness), and energy absorption to failure outline the strength of the measured bone or part of it (Turner 2002). Loading and fatigue tests can be performed with animal or cadaver bones in situ. In both research and clinical practice, the current method-of-choice to assess bone strength and fracture risk is based on noninvasive assessment of bone mineral by dual energy x-ray absorptiometry (DXA) (Marshall et al. 1996, Genant et al. 1996, Genant 1998). Though bone mineral measurements are useful, the regional averaging obscures structural differences or alterations that may be critical determinants of bone strength (Beck et al. 1990). Thus, measurements of bone mineral should be complemented by methods that provide mechanically more relevant information on bone structure. However, despite the evidence of the importance of structural architecture in the assessment of bone integrity, it is not yet fully understood whether or which structural measures will prove to be indices of fracture likelihood in a complex structure like the femoral neck (Beck et al. 1993, Faulkner et al. 1993, 1994). In turn, the lack of harmless, accurate, reproducible and inexpensive measurement techniques that can measure both material and structural properties of different parts of skeleton is evident (Genant 1996, Gilzans 1999, Currey 2001).

#### *Dual energy X-ray absorptiometry*

DXA was introduced commercially in 1987 and it determines bone mineral content and areal bone mineral density (aBMD). Areal BMD is calculated as the quotient of the BMC and projected area (Figure 4). DXA has many benefits; it is precise (at least in short term), examination times are short, radiation dose is low, and aBMD predicts the fracture risk at the population level. Thus, it is suitable for most clinical purposes (Genant 1998). In addition, in most cases DXA is the only noninvasive method available to assess osteoporosis. The “normalization” of BMC by the projected area partially reduces the effect of body size (Genant et al. 1996). While minimizing the differences between large-boned and small-boned individuals, aBMD facilitates the assessment of what is “normal” in the process of screening, which actually has been a principal target market for the technology (Heaney 1996). Although aBMD values are turn out to be good predictors of whole bone strength and the fracture risk at the population level they cannot identify those individuals who will eventually get a fracture (Marshall et al. 1996).

To improve the predictive value of densitometric data, analytic strategies have been proposed to assess bone’s apparent volumetric density and structure. Assuming cylindrical shape of bone, bone mineral apparent density (BMAD) can be calculated as BMC per estimated total bone volume (Kazman et al. 1991, Carter et al. 1992). This adjustment for site-specific estimate of bone size can

alleviate the effects of variation in regional bone size and shape during the skeletal growth (Katzman et al. 1991). BMAD has not achieved popular use. One reason for this can be its inability to improve the predictive value of aBMD for future hip fractures (Cummings et al. 1994). Whereas, the hip strength analysis (HSA) has been shown to predict breaking strength of the femoral neck and hip fracture better than aBMD alone (Beck et al. 1990, Faulkner et al. 1994, Crabtree et al. 2002). HSA might prove to be a reasonable enhancement of DXA densitometry in clinical practice and interestingly, this method has recently obtained a footing in the field of physical activity and pediatric bone research (Petit et al. 2002).

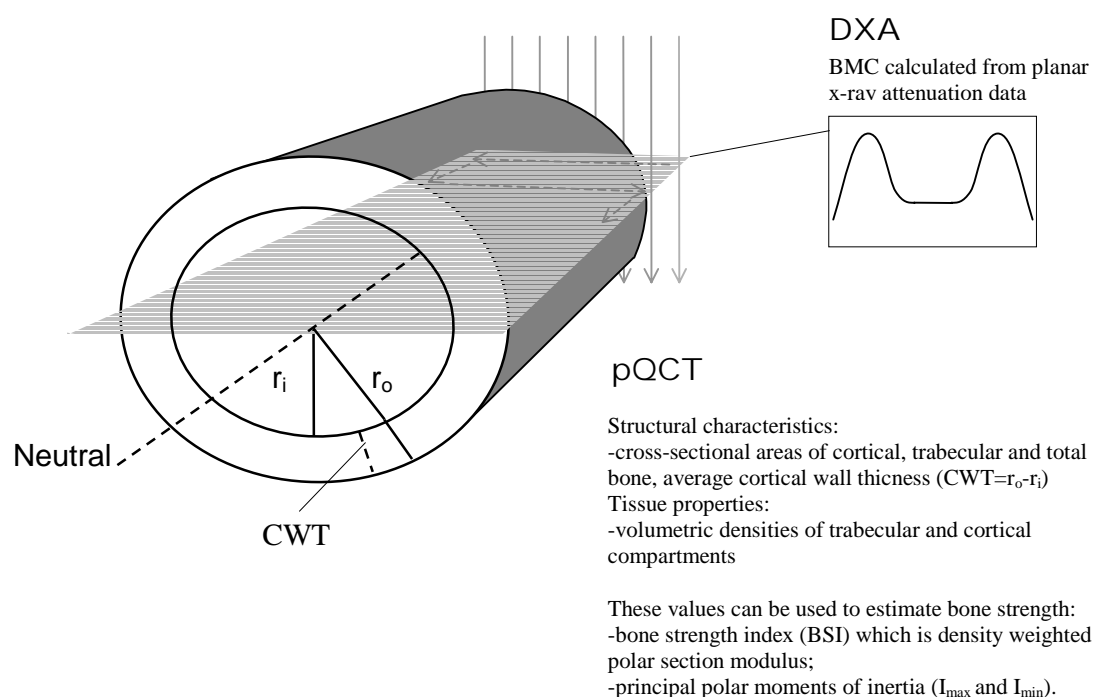
However, the planar nature of DXA makes the assessment of the geometry and true composition of bone impossible, and the evaluation of bone fragility of an individual is likely to be an approximation at best (Sievänen 2000a). In addition, DXA measurements are subjected to considerable patient-specific inaccuracies (Bolotin et al. 2001), and can thus seriously mislead the diagnostic or prognostic interpretations of individual bone fragility (Bolotin and Sievänen 2001). Due to these facts, the relevance of the areal BMD as a surrogate of bone fragility at individual level has been challenged, and the need for more sophisticated noninvasive methods to characterize bone accurately has been clearly brought up (Beck 1996, Järvinen et al. 1999, Faulkner 2000, Currey 2001, Bolotin and Sievänen 2001).

### *Quantitative computed tomography*

Compared to densitometry, the incomparable advantage of quantitative computed tomography (QCT) is its ability to determine, in principle in three dimensions, the (apparent) volumetric densities of both trabecular and cortical compartments at any skeletal site (Genant et al. 1996). However, QCT has been principally employed to determine trabecular bone density in the vertebral centrum because of this ability to selectively assess the trabecular compartment and its changes (Genant et al. 1996). There is not yet clinically accepted QCT technique for the hip measurements due to the complex architecture of the proximal femur, and thus, virtually all clinical assessment of the proximal femur integrity is preformed with DXA (Genant et al. 1996).

Due to the high radiation dose, cost and inaccessibility of QCT scanners, its practical application for bone measurements has been limited. Whereas peripheral QCT (pQCT) with lower radiation dose and cost, have been found to be useful for the measurements of appendicular skeleton (Genant et al. 1996, Sievänen et al. 1998). Peripheral QCT is also suitable for use in young populations (Gilsanz 1999). In clinical use, the most common measurement site is distal radius (Genant et al. 1996). The most sophisticated pQCT scanners also incorporate a multislid data acquisition capability covering a larger bone volume (Genant et al. 1996). The measurement of several slides could potentially give more representative three dimensional picture of bone size, structure and entire bone strength, and would therefore reflect the bone's clinical status more accurately. The importance of the measurement technique

capable to obtain both cross-sectional area of cortical shell (Figure 4), and the apparent density of both cortical and trabecular compartments could optimize the diagnostic and prognostic sensitivity of bone integrity (Spadaro et al. 1994, Gilsanz et al. 1995). Furthermore, the importance of each surrogate of bone strength may vary site specifically, and relate to the customary loading environment in the specific bone site.



**FIGURE 4** Illustration of tubular bone and its biomechanical properties that can be measured by DXA or pQCT. When the shape of bone is assumed to be a cylinder, the cross-sectional area of bone is more important for resisting loads in bending or torsion than are its mass or density (Einhorn 1992). Ideally, in bending or torsion, bone should be distributed as far away from the neutral axis of the load as possible. Geometrically, this distribution of mass around the center of gravity of a structure is described in bending by the cross-sectional moment of inertia, (CSMI). Cross-sectional moment of inertia (CSMI) is proportional distribution of mass around the neutral axis, and defined as follows:  $CSMI = \pi/64 (r_o^4 - r_i^4)$ . Similarly, in torsion, deformation would be resisted more efficiently if bone mass were distributed further away from the neutral axis of loading (polar moment of inertia) (Einhorn 1992).



## 2.2 Bone mass, structure and strength from childhood to adulthood

Current knowledge about the differences in structure, mass and apparent density of bone by age is based on cross-sectional data from former radiogrammetry studies (Garn 1972), and more recent QCT- and pQCT-comparisons (Gilsanz et al. 1988, 1991, 1994, Lu et al. 1996, Mora et al. 1994, 1999, Neu et al. 2001a,b, Schoenau et al. 2001). QCT- and pQCT data has been obtained mainly from the spine, distal radius, and femoral shaft of both genders with a large range of age. A relative increase in cortical BMC in children was similar in both the genders, whereas the increases in bone size and the surrogates of bone strength were higher in boys already at early puberty (Gilsanz et al. 1994, Neu et al. 2001a, Schoenau et al. 2001). Greater strength parameters reflect the fact that during rapid skeletal growth boys are able to add more bone on the periosteal surface than girls. Instead, girls either add bone on the endocortical surface (Garn 1972, Parfit 1994, Gilsanz et al. 1994), or diminish the endocortical removal of bone. Either way, this will have a minor effect on bone strength as compared to periosteal apposition. BMC is greater in men because periosteal modeling continues longer in boys than in girls, whereas slightly greater BMD in women has been explained to be due to the maintained size of the marrow cavity in girls compared to the increase in boys (Neu et al. 2001a). The purpose of the maintenance of this mechanically less effective endocortical bone in female puberty might be to create a reservoir of calcium for future pregnancy and lactation (Parfit 1994, Carter et al. 1996, Frost 1999, Schoenau et al. 2001).

In the spine, trabecular BMD seems to peak around the time of cessation of longitudinal growth and epiphyseal closure. Thus puberty and related events have explained to be the major determinants of the increased cancellous bone density in both genders (Gilsanz et al. 1988, 1991, 1994, Mora et al. 1994, Lu et al. 1996). Whereas in the distal radius, trabecular BMD seems to increase after 15 years of age in boys only, resulting in higher trabecular BMD in men than in women (Neu et al. 2001b).

During aging endosteal resorption of bone is compensated by periosteal bone formation that will lead to an increased outer cortical diameter (Smith and Walker 1964, Ruff and Hayes 1982, 1988, Martin and Atkinson 1977, Bouxsein et al. 1994, Beck et al. 2000). Although the net effect may be cortical wall thinning, the distribution of the bone material further from the neutral axis improves bone's resistance to bending and torsional loads.

It has been suggested that extrinsic mechanical influences (that seems to remain active throughout an individual's lifetime) may become the fundamental processes responsible for changes in bone cross-section when the contribution of purely biological growth processes diminish with age (Carter et al. 1996). The premise for this argument comes from a mathematical model that shows that mechanobiological stimuli are the sole regulators of changes in long

bone cross-sectional geometry once the biologic contribution has disappeared (van der Meulen et al. 1993).

### **2.2.1 Exercise and the growing skeleton**

Throughout growth, but particularly during adolescence, the ability of bone to adapt to mechanical loading seems to be much greater than after maturity (Forwood and Burr 1993). This may be the main reason why the effect of physical activity on bone mineral is greater in cross-sectional studies of young athletes than in longitudinal studies of previously sedentary adults (Parfitt 1994). However, the effects of mechanical loading on the distribution of bone mineral, bone size, structure and BMD in the growing and mature skeleton (and within and between genders) is rather poorly understood. Many competent reviews (Bailey et al. 1996, Barr and McKay 1998, Khan et al. 2000, Bass 2000, McKay and Heinonen 2002) and a recent book (Khan et al. 2001) suggest that physical activity during growth can increase bone accrual. If accelerated accrual continues it may enhance peak bone mass and, thus, is important to bone health. Nevertheless, the possible redistribution of this exercise-induced bone mineral (which mainly determines the mechanical competence of the whole structure) cannot be resolved via BMC or aBMD measurements only (Sievänen 2000). Although the exercise-induced BMC gain was shown to be twice as great if obtained in adolescence compared to that obtained in adulthood (Kannus et al. 1995), the benefit in bone strength might turn out to be even greater if bones' mechanical competence could be assessed more appropriately.

The literature provides one cross-sectional comparison of 7-11 year-old gymnasts and control children using pQCT to assess exercise-induced alterations in growing bone (Dyson et al. 1997). Both apparent trabecular and cortical BMD were significantly greater in the gymnasts. Also, the total cross-sectional area of the distal radii was 11% larger than that of controls but this difference was not statistically significant. Trabecular area was significantly greater in the forearm, suggesting that bone material had shifted towards mechanically more competent structure (Dyson et al. 1997). Cross-sectional MRI comparison of mid-femur geometry and biomechanical properties between 15- to 18-yr-old female athletes showed that runners had more favorable geometric and biomechanical bone characteristics compared with swimmers and cyclists (Duncan et al. 2002). In contrast, after a 9-month jumping intervention neither pQCT-derived cortical density nor the CSA of the tibial midshaft showed significant exercise-induced improvement although on average 4 % greater DXA-based BMC gain was seen in premenarcheal trainees compared to that of controls at the lumbar spine and femoral neck (Heinonen et al. 2000).

However, greater BMC accrual has been reported in physically active children (Bailey et al. 1999), and augmented aBMD accrual in the trainees of various exercise interventions (McKay et al. 2000, Witzke and Snow 2000, Sundberg et al. 2001, McKelvie et al. 2001, 2002). Increased bone area at the femoral neck was also noted after 8-10 months in prepubertal trainees (Morris et al. 1997, Fuchs et al. 2001).

In addition, bone densitometry-derived surrogates have been used to estimate the effect of exercise-interventions on bone mineral apparent density (BMAD) at the lumbar spine and section modulus at the femoral neck and shaft regions (Morris et al. 1997, Bradney et al. 1998, Petit et al. 2002). Increased cortical thickness at the femoral midshaft (due to decreased endocortical diameter) was obtained in the trained boys after eight months of weight-bearing physical activity. In a recent Canadian intervention, exercise increased the DXA-derived section modulus at the femoral neck, and since the outer diameter of bone remained unchanged, training seemed to have reduced endosteal expansion within the bone (Petit et al. 2002). However, when interpreting these results the limitations of planar DXA-measurement technique should be kept in mind.

Most of these studies assessed the effect of exercise on prepubertal or early pubertal skeleton alone. Therefore, it has been discussed whether the most optimal age period to influence bone by exercise is during prepuberty, or at the puberty (i.e. in girls at the time before the menarche). A recent study by Heinonen et al. (2000) focused on this issue and showed that 9-month jumping intervention led to an increased bone gain in girls who were premenarcheal whereas girls who were menarcheal before or during the intervention did not differ from their controls. Within pre-menarche, McKelvie et al. (2001) found that bones of the early pubertal girls (Tanner II) responded to exercise training while prepubertal trainees did not differ from their controls. At Tanner stages II to III, many endocrinological factors related to growth and maturity are peaking (Mauras et al. 1996, Dunger et al. 1991, Bonjour et al. 2001, Sommerfeldt and Rubin 2001) giving support to the opinion that the period before menarche when growth accelerates may be an effective time to maximize the impact of exercise on bone.

A study of young female tennis players supports this contention. Haapasalo et al. (1998) showed an advantageous side-to-side BMC difference at the humerus, i.e. exercise-induced bone gain, was not achieved until Tanner stage II and III. In addition, the amount of training was not related to the exercise-induced bone gain before Tanner stage III (Haapasalo et al. 1998).

During childhood and adolescence bone growth has a different tempo at different parts of the skeleton (Bass et al. 1999, 2000). This suggests that simplistic conclusions may be inappropriately drawn if repeated bone measurements are obtained at one site only. However, despite the scientific debate and many unanswered questions, the whole period of skeletal growth represents a unique window of opportunity to maximise peak bone mass (Bass 2000, Khan et al. 2001). Whether exercise during the growth can influence bone mass distribution and form a stronger bone structure, remain key questions. As importantly, we do not know whether these exercise-induced alterations in bone structure are permanent. That is, does a decrease in, or withdrawal from exercise destroy all the benefits? These important questions were integrated into the aims of this thesis.

### 2.2.2 Exercise and the mature skeleton

Much of the clinical evidence for an effect of exercise on mature bone comes from cross-sectional comparisons between athletes and their age-, height-, and weight matched controls (Schoutens 1989, Smith and Gilligan 1991, Suominen 1993, Chilibeck et al. 1993, Heinonen et al. 1995, Snow et al. 1996). In these studies, the strength, power, and impact-type trained athletes showed a higher aBMD (or BMC) at the loaded skeletal sites compared to endurance athletes, or physically active and sedentary controls. Intervention studies in pre- and postmenopausal women have, in turn, shown either small exercise-induced aBMD increases (2-5%) (Dalsky et al. 1988, Bouxsein and Marcus 1994, Forwood and Burr 1993, Drinkwater 1996, Heinonen 1996, Ernst 1998, Kelley et al. 2001), no effect (Friedlander et al. 1995, Lohman et al. 1995), or even bone loss (Rockwell et al. 1990) at different skeletal sites. At the femoral neck, a meta-analysis of six prospective intervention studies of aerobic exercise in postmenopausal women showed an, on average, 2.4% aBMD increase compared to controls (Kelley 1998). The modest intervention effects in aBMD have been explained by the short duration of the intervention; insufficient type, intensity, or frequency of the training; or measurement of a less loaded bone site. Also, comparing the results of an exercise trial to the bone benefits seen in highly trained top-athletes (who have been trained hard for several years and usually since adolescence) is not optimal.

Further, the lack of aBMD increases reported in some interventions could be due to the limitations of planar densitometry. Some experimental training studies have shown improvement in mass distribution, dimensions, or strength of loaded bones, without a corresponding change in bone mass or aBMD (Woo et al. 1981, Raab et al. 1990, Järvinen et al. 1998). Respectively, a 6-month moderate-intensity exercise intervention in postmenopausal women showed no effect on the integrated bone mass but seemed to lead to both periosteal bone apposition and corticalization of the trabecular tissue at the distal radius (Adami et al. 1999).

Alteration in bone structure of the adult skeleton may be related to the process of aging, in addition to mechanical loading. A comparison of pre- and postmenopausal women with habitual physical activity at least twice a week to their inactive counterparts showed that the influence of physical activity to bone CSA and BSI at the tibial and radial shafts become apparent not until older ages (Uusi-Rasi et al. 2002a). Exercise, thus, might have a role in the formation of compensatory structures by increasing the cortical enlargement periosteally and by preventing age-related bone loss at the endosteal surfaces. There is some experimental data that supports this (Gabrie et al. 1999).

Recently, the effects of extreme impact loading and long-term strength training on mass distribution, structure and strength of bone have been demonstrated in male triple jumpers and female weight lifters (Heinonen et al. 2001a, 2002). The purpose of these studies has been to clarify the ultimate upper limits of the effects of mechanical loading on human bone. Compared to the matched control group, over 50% greater cortical area and cortical wall

thickness led to 31% higher bone section modulus at the jumpers' distal tibia (Heinonen et al. 2001a). Also, the apparent trabecular density at the distal and proximal tibiae was 18% and 41% higher in the jumpers than controls, whereas the cortical density of these sites did not differ between groups (Heinonen et al. 2001a). Similarly, in female weightlifters the cortical area of the distal radius was almost 40% greater than that of controls, while a 10% difference was found in trabecular density (Heinonen et al. 2002). According to these observations, a rather wide range of adaptation seems possible, and most importantly, exercise seems to provide great benefit for bone strength, the bottom line. In this context, however, we must keep in mind that many confounding factors related to selection bias and athletic life-style may obscure the conclusion drawn from these cross-sectional comparisons.

Observations on the evidence of hypertrophy of the tennis players' playing arm bones emphasizes that adaptation to loading is caused by changes in the local functional environment of bone (Jones et al. 1977, Montoye et al. 1980, Dalen et al. 1985, Pirnay et al. 1987, Krahl et al. 1994). From an alternate perspective, the cross-sectional comparisons of tennis players revealed that the players' nondominant bone site showed the lowest BMC values of all (Kannus et al. 1995, Haapasalo et al. 1996, 1998). Also, constantly lower aBMD in the unloaded skeletal region, the upper part of the skull, has been reported in the former as well as active athletes and is thought to be due to bone mass shift from the unloaded skeletal regions to their loaded counterparts (Karlsson et al. 1995, Magnusson et al. 2001). Furthermore, recent follow-up of both pre- and postmenopausal women showed that radial bone loss (an unloaded bone site) may accompany high physical activity (Uusi-Rasi et al. 2001, 2002b). Finally, the use of the upper skull aBMD as a reference for nonloaded bone region is predisposed to many artefacts that are related to the shape of the head and its positioning during measurement (personal communication, Harri Sievänen 2002). Although this 'stealing phenomenon' is fascinating, further evidence from controlled, prospective follow-up studies is needed to ascertain the causality between mechanical loading and slight bone loss from unloaded sites.

### **2.3 Maintenance of exercise-induced bone gain**

Exercise-induced bone gain may afford important protection against age-related bone loss, especially if exercise began during the growing years, when the benefit to peak bone mass may be maximized (Virvidakis et al. 1990, Kannus et al. 1995, Haapasalo 1998). Although childhood or adolescent bone gain cannot be expected to provide total prevention against age-related accelerated bone loss, it may, at least in theory, temper the severity of bone loss and prevent a critically low bone mass that will predispose to fractures (Bailey et al. 1996, Heaney et al. 2000, NIH Consensus Statement 2000). However, the current literature gives very contradictory findings concerning the maintenance of the exercise-induced bone gain after the activity is decreased or completely stopped.

### 2.3.1 Evidence for the maintained benefit

Cross-sectional comparisons of former athletes and their controls provide evidence that at least some residual bone health benefits appear to be maintained into adulthood (Table 1). Many of these studies assessed the bone health of female gymnasts and dancers since their intense training and slender body type predispose them to many risk factors (e.g. amenorrhoea) for osteoporosis later in life.

However, even higher aBMD values at the lumbar spine, proximal femur, and whole body were found in former gymnasts compared to their controls when the differences in current and past physical activity levels were controlled via analysis of covariance (Kirchner et al. 1996). Another study with young former gymnasts found similar aBMD at these sites compared to controls even if gymnasts reported late pubertal development and irregular menstrual patterns, moreover, aBMD at arm was in favor of former gymnasts (Lindholm et al. 1995). Similarly, compared to controls, Bass et al. (1998) reported 0.5-1.5 SD higher aBMD at the lumbar spine, hip, and arm in former gymnasts who had retired on average 8 years previously. Diminution was also not noted across the years since retirement, despite the lower frequency and intensity of exercise (Bass et al. 1998). Similarly, despite many historical risk factors for osteoporosis reported by retired dancers (mean age 51 years), aBMD at weightbearing sites was the same as compared with size- and age-matched controls (Khan et al. 1996). However, current activity was greater among dancers compared to controls. Interestingly, dancers' self-reported weekly hours of ballet class undertaken at age 10-12 years was positively associated with current aBMD differences at the hip between dancers and controls (Khan et al. 1998). Furthermore, this association was unaffected after adjustment for covariates including years of full-time ballet and current physical activity (dancers were twice as active as controls).

Former weightlifters, in turn, were compared with nonathletic controls and demonstrated an aBMD benefit until 65 years of age (Karlsson et al. 1995 and 1996), whereas former soccer players seem to differ from their controls until age 50 to 60 (Karlsson et al. 2000, Magnusson et al. 2001).

Although these retrospective studies provide promising evidence that the exercise-induced bone health benefit is maintained, there are many confounding factors that may obscure the conclusion. Results can be biased because the quantity and quality of physical activity of former athletes or dancers during childhood or adolescence are difficult to evaluate retrospectively – as are their other bone-affecting living habits at that time or later. Additionally, the amount of bone gained by exercise prior to cessation of training is not known. Also secular changes in height, bone size, and training regimens are evident in cross-sectional comparisons across large age range. Thus, the likelihood of pure selection bias when comparing former athletes and their controls cannot be excluded. Although athletes in these studies had ceased their active career, they appeared to be more active than sedentary controls.

TABLE 1 Cross-sectional comparisons of bones of retired athletes and their controls

Reference	Subjects, age	Time since retired	Bone-site (method)	Results compared to controls
Huddleston et al. 1980	Tennis players, over 70 yrs	40 yrs, still playing on average twice a week	Midradius (DPA)*	13% side-to-side BMC difference
Karlsson et al. 1995	49 male weight lifters, 50-79 yrs 66 age-matched controls	Mean 30 yrs (range 5-70yrs)	Total body, LS, hip (DXA)	9-17% greater aBMD (after age 65 no difference)
Lindholm et al. 1995	19 female gymnast, 19-29 yrs 21 controls	9-10 yrs	Arm, leg, hip, LS total body (DXA)	1% greater aBMD only at the arm
Duppe et al. 1996	34 senior male football players, 18-28 yrs 25 former players, 34-84 yrs 57 controls, 32-42 yrs	Mean 9.7 yrs	Total body, LS, prox femur (DXA)	4-9% greater aBMD, except at LS, no difference between senior and former players
Kirchner al. 1996	18 former female gymnasts, mean age 36.3 yrs 15 controls	Mean 18 yrs	LS, FN, Ward's triangle and total body (DXA)	9-22% greater aBMD
Khan et al. 1996	101 retired elite female ballet dancers, mean age 51 years 101 controls	Mean 26 yrs	Prox femur, LS, radius (DXA)	No difference, except at radius 3% lower aBMD
Khan et al. 1998	99 female ballet dancers at childhood, mean age 51 yrs 99 controls	On average 40 yrs	FN, hip (DXA)	Hours of ballet associated with a aBMD difference between controls
Bass et al. 1998	36 retired female gymnast, 18-35 yrs 15 matched contols	Mean 8 yrs, Range 1.5-20 yrs	Total body, FN, WT, troch., LS, arm, leg, skull, (DXA)	6-16% greater aBMD, except at the skull
Karlsson et al. 2000	22 active male soccer players, 17-34 yrs 128 formet players, 138 controls	Mean 23 yrs, Range 1-65 yrs	Legs, FN, arm, (DXA)	Higher leg aBMD until retired for 25 years, if adjusted for current activity and body composition the benefit remained until age 70
Magnusson et al. 2001	128 former soccer players, 19-85 yrs 138 controls, 19-80 yrs	Mean 23 yrs, Range 1-65 yrs	FN, arm, skull (DXA)	Higher aBMD in FN until age 50, lower in skull until age 70

DPA= Dual photon absorptiometry

### **2.3.2 Evidence for a diminished bone health following detraining**

Detraining studies with pre- and postmenopausal women have suggested that the benefits of exercise may be lost after the end of the intervention (Table 2). However, in two of these studies only lumbar spine aBMD was measured (Dalsky et al. 1988, Iwamoto et al. 2001) and in general the number of detrained subjects was 15 or fewer, except in the study by Winters et al. (2000). In this study of 29 premenopausal women, spinal, femoral and total body aBMD changes during the 6-month detraining period were evaluated using a within-subjects design for detrainees and controls separately. This raises the question of whether results would have been different if detraining effects had been analyzed in the same way as the training effects, i.e. by between-groups analysis of covariance. The unilateral training-detraining studies, in turn, showed either no training effect (Heinonen et al. 1996), or a significant improvement was seen only in one of the several bone sites measured (Vuori et al. 1994). Thus, the effect of detraining could not be assessed.

It has been proposed that during the years of skeletal growth exercise-induced bone gain may lead to permanent positive adaptations in bone structure that later interruption of the training stimulus would not abolish the benefits (Parfit 1994, Forwoor and Burr 1995). However, the only follow-up report in growing children is a comparison of 6-month-change in calcaneal SOS and BUA values by ultrasonography between active and retired gymnast and runners (Lehtonen-Veromaa et al. 2001).

Thus, there is a clear need to evaluate whether exercise-induced bone gain is maintained into adolescence and adulthood. Furthermore, the effect of detraining should be assessed among athletes after cessation of their career, as well as among former participants of exercise intervention trials.



TABLE 2 Follow-up bone studies after the end of the exercise intervention

Reference	Subjects, age	Length of training (T) and detraining (D)	Type of training	Bone-site (method)	aBMD/BMC change
Dalsky et al. 1988	28 trainees, 55-70 yrs 15 detrainees 32 controls	T: 9-22 months D: 12-13 months	Walking, jogging, star climbing	LS (DPA)	T: +6% D: -4.8%, 1.1% above baseline
Vuori et al. 1994	12 trainees, 19-27 yrs 12 controls	T: 12 months D: 3 months	Unilateral leg press	LS, FN, femur, patella, tibia, calcaneus (DXA)	T: patella +1.5% D: return to baseline
Heinonen et al. 1996	13 trainees, mean age 23 yrs 19 controls	T: 12 months D: 8 months	Unilateral arm strength training	Humerus, ulna radius (DXA)	T: no significant training effect
Winters and Snow 2000	29 trainees, 30-45 yrs 22 controls	T:12 months D:6 months	Impact + resistance	Whole body, FN, troch.,LS (DXA)	T: troch; +2.6% D: +1.7% above baseline, NS
Snow et al. 2001	8 gymnast, 19 yrs	T: 2*8-month D: 2*4-month off-seasons	Gymnastics	Whole body, FN, troch,LS (DXA)	T: LS +4%, FN +2% D: both -1.5%
Iwamoto et al. 2001	8 trainees, 53-77 yrs 7 detrainees 20 controls	T: 24 months D: 12 months	Brisk walking and calisthenics	LS (DXA)	T: +4% D: +2% above baseline, NS
Lehtonen-Veromaa et al. 2001	52 active gymnast, 11-17 yrs 9 retired gymnast, 58 active runners, 12 retired runners 55 controls	T:1-year follow-up, D: on average 6 month	Gymnastics and running	Calcaneus (ultrasonography)	Change (%) in BUA, SOS: Active gymnasts +8, +3 NS Retired gymnasts +2 NS,-6 NS Active runners +6, +7 Retired runners +1 NS, -13 Controls +6, +4

## 2.4 Summary of the literature

Dynamic rather than static loading drive skeletal adaptation, and only a brief duration of loading is required to initiate an adaptive response. Customary loading environment with similar or repetitive loading signals is likely to make bone cells less responsive to activity. Evidence of local hypertrophy of the loaded humerus in tennis players emphasized the focally-mediated adaptation due to changes in the local functional environment. However, most clinical evidence for an exercise-induced bone benefit comes from cross-sectional comparisons of athletes and their controls, and from intervention studies, which examined the effect of loading on BMC or aBMD accrual only. Although knowledge about how the skeleton adapts to mechanical loading has increased during recent decades, the prevalence of DXA-measurement technology has directed the focus away from the fundamental principles of the bone integrity, overlooking the accurate assessment of bone geometry and structure. In contrast, the link between bone strength and the amount of bone material (BMC) is indisputable. Respectively, the positive effect of exercise on bone mass accrual has been confirmed, especially if exercise is performed during the growing years. However, other factors that underpin the observed increases in bone material, and the effect of changes in bone mass distribution and structure on bone integrity, the bottom line, cannot be determined from DXA studies where aBMD is the outcome.

Experimental studies have suggested that increased bone mass is a function of bone apposition on the periosteal surface, whereas endosteal apposition is possible during growth only. In the growing bone, exercise-induced bone mass accrual appears greater compared to the adult skeleton. However, whether mechanisms of bone acquisition, changes in trabecular and cortical compartments or architectural properties between and within different skeletal sites, vary in growing and mature bone (and between genders and races) is not known. In addition, the possible differences in these changes have been suggested to explain the discrepancies regarding whether exercise-induced bone gain is maintained (cross-sectional comparisons support a maintained bone benefit, whereas the follow-ups of the exercise interventions show a bone loss). Thus, exercise-induced changes in bone structure and strength in young and old individuals may well be couple with the maintenance of these benefits. However, these issues have been poorly examined and are not well understood. Thus, an examination of lasting benefits to bone health following cessation of exercise is the primary aim of the current thesis.

### **3 PURPOSE OF THE STUDY**

The objectives of this thesis were to investigate the effects of long-term mechanical loading on mass, size and mechanical strength of bone in male and female racquet sports players, to evaluate the maintenance of exercise-induced bone gain in these players during the following years of reduced training, and to assess bone maintenance after exercise interventions in pubertal girls and premenopausal women.

More specifically, the aims of the individual studies were the following:

- I To compare side-to-side differences in pQCT-derived surrogates of bone strength, i.e. tissue and structure at cortical and trabecular bone sites in the humerus and radius of male and female racquet-sports players to that of the nonplaying controls (studies I and II).
- II To evaluate whether loading-induced alterations in bone size, structure and density differed between female players who had started training during the growing years versus during adulthood (study II).
- III To assess whether the exercise-induced BMC gain among the above noted players was lost with reduced training, and whether the bone response to decreased training differed if the playing career has been started before or at puberty rather than after it (studies III and IV).
- IV To determine the effect of a jumping intervention on subsequent bone accrual in growing girls and to evaluate the maintenance of the exercise intervention-induced bone gain in premenopausal women during the subsequent years of detraining (studies V and VI).

## 4 METHODS

### 4.1 Subjects and design

Altogether 223 persons were involved in the study series. The subjects were male and female racquet sport players and their age-, weight-, and height-matched controls, nonathletic peripubertal girls, and sedentary premenopausal women.

Number of subjects in the different studies and their selected characteristics at the baseline measurement are presented in the Table 3. Specific information about study design is provided in the original reports.

TABLE 3 Characteristics of the subjects, mean (SD)

Study	Subjects	N	Age, years	Height, cm	Weight, kg
II, IV	Female racquet sports players	64	29.5 (12.7)	167.0 (5.6)	61.5 (6.5)
	Controls	27	28.6 (10)	166.6 (4.7)	63.0 (9.6)
I, III	Male tennis players	13	26.0 (5.1)	179.4 (4.4)	71.2 (7.4)
	Controls	13	26.2 (5.9)	180.9 (7.0)	75.9 (5.2)
V	Peripubertal girls	50	12.8 (1.5)	154.6 (10.4)	46.4 (11.8)
	Controls	49	12.2 (1.6)	153.5 (9.4)	44.9 (11.2)
VI	Premenopausal women	34	39.6 (2.2)	164 (0.1)	61 (7.0)
	Controls	31	38.4 (2.7)	165 (0.1)	61 (7.6)

## **4.2 Measurements**

### **4.2.1 Questionnaires**

Information regarding living habits and health status such as physical activity or training history (data on starting age and years of active playing, training sessions per week, duration of each session), possible injuries, menstrual status, medication, diet, consumption of alcohol, smoking, and known diseases was obtained with detailed questionnaires. In girls, pubertal status and sexual maturity was determined by visual inspection of the subject using the development pictures of Morris and Udry (1980) illustrating the five Tanner stages according to breast development and pubic hair distribution. Girls completed a 4-day food diary, and daily dietary and calcium intake was calculated using the Micro Nutrica software (Social Insurance Institution, Helsinki, Finland).

### **4.2.2 Anthropometric assessment and muscle strength and power measurements**

Height (cm) and weight (kg) were measured on all subjects, whereas circumferences of upper extremities were gathered from tennis players and their controls only. Likewise, isometric grip strength was measured with a standard grip strength-meter and elbow extension and flexion forces were determined with an isometric dynamometer (Digitest Inc., Muurame, Finland) from the tennis players and their controls (studies I-IV) (Heinonen et al. 1994).

In study V, the baseline and follow-up maximal isometric strength of the leg extensors was measured with a strain gauge dynamometer at a knee angle of 90° (Heinonen et al. 1994). In addition, according to the Eurofit test battery (1993), a standing long jump test was performed to evaluate leg power, and agility of the subjects was tested by a shuttle run test. In the latter test, the subject ran as fast as possible from the starting line to line (5 m apart) and then returned to the starting line, crossing both lines with both feet. This cycle was repeated five times when the total running distance equalled 50 m.

In study VI, maximum isometric leg extension strength was measured with a strain gauge dynamometer at a knee angle of 90° (Heinonen et al. 1994), and leg extensor power with a counter movement jump test, first without, and then with, an additional weight of 10% body weight. Agility and dynamic balance were assessed by a figure-of-8 running test (Tegner et al. 1986).

### 4.2.3 Bone measurements

#### *DXA measurements*

Dual-energy X-ray absorptiometry (XR-26, Norland Corporation, Wisconsin, USA) measurements were performed using the standard bone measurement procedure of our laboratory (Figure 4). In vivo precision of BMC and aBMD measurements has been shown to be around 1% (Sievänen et al. 1992, 1993, 1996). Our quality assurance program monitored the scanner performance and no scanner drift was observed during the follow-ups (Sievänen et al. 1994). Information regarding the measurement sites, BMC and aBMD variables, and their reproducibility is given in the original reports.

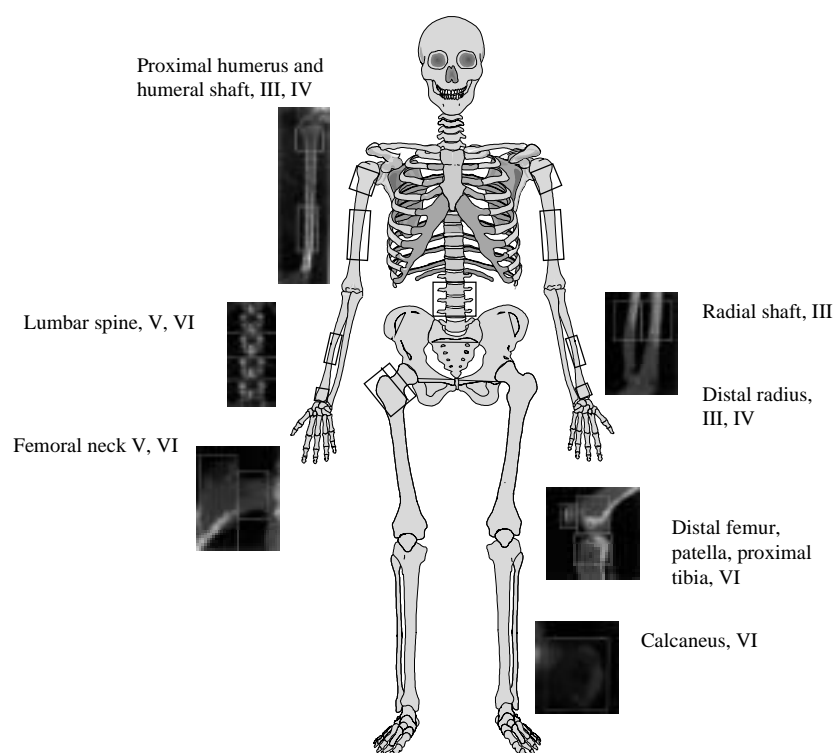


FIGURE 5 DXA-measurement sites: humerus, radius, lumbar spine, proximal femur, area of knee joint and calcaneus. The Roman numeral corresponds with the study in which the site was measured.

#### *PQCT measurements*

The structural characteristics of bone were measured with Norland/Stratec XCT 3000 pQCT scanner (Stratec Medizintechnik GmbH, Pforzheim, Germany), which has shown to be highly precise, linear, and stable system for bone measurements (Sievänen et al. 1998). The pQCT measurements were performed at three different sites in the humerus and two sites in the radius in male tennis players. In the large group of female players, the measured sites were limited to the humeral shaft and distal radius. The in vivo precision of the pQCT-measurements has been shown to vary from 0.5% to 6% at the humerus and

radius (Sievänen et al. 1998). Specific information about the measurement sites, measured variables (BMC, CoA, TrA, TotA, CoD, TrD, BSI<sub>t</sub> and BSI<sub>c</sub>) and their reproducibility are given in the original reports.

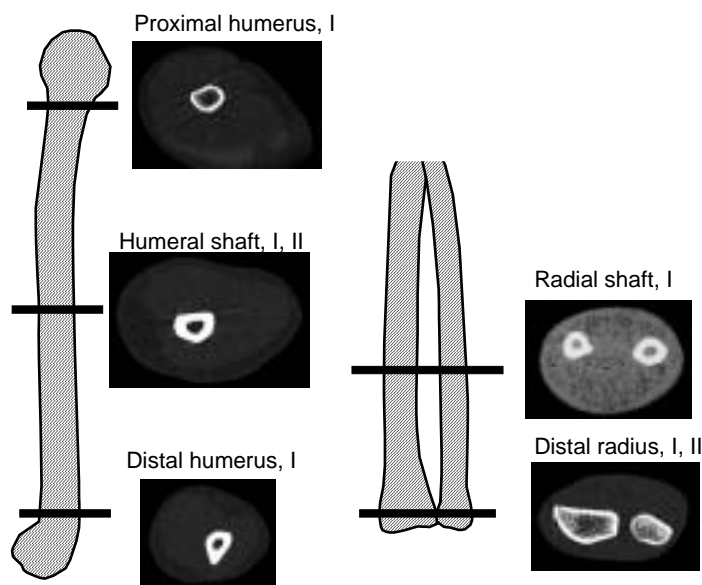


FIGURE 6 The pQCT- measurement sites at the humerus and radius, the roman numbers indicating the study the site was measured.

### 4.3 Statistical methods

Mean and standard deviation (SD) are provided as descriptive statistics throughout the study. In studies I, III and IV, the relative side-to-side BMC difference was calculated by dividing the dominant-to-nondominant side BMC difference by the nondominant side BMC value and then multiplying the outcome by 100. In study II, the relative side-to-side differences (%) were obtained through the log-transformation of the variables and then by the antilog-transformation of the parameter estimates. The results were then given as percentages.

The side-to-side BMC differences within the study groups were analyzed using the paired t-test (studies I-IV) and the difference between the groups was tested by the two-sample t-test (study I) and by the analysis of covariance (study II) and the Student's two-sample t-test (study III). The post-hoc group comparison in study II was performed with Sidak's method.

Change in the relative side-to-side BMC difference across the three study groups (young starters, old starters and controls) in study IV was analyzed using the analysis of variance with repeated measures and the post-hoc group comparisons (adjusted for multiple comparisons) were done by the Scheffé's method. The associations between changes in the training variables of the

players and changes in their relative side-to-side BMC differences were described with the Pearson's product moment correlation coefficients (study III) and the non-parametric Spearman rank correlation coefficients (study IV).

In study V, the strongest predictors of BMC accrual during the 20-month follow-up were identified by multiple regression analysis. Participation in the jumping intervention (yes/no) was added into the model to evaluate the effect of former participation in the jumping intervention. In study VI, general linear models (GLM) with restricted maximum likelihood estimation were used to estimate the intergroup aBMD differences (adjusted for the baseline values) at 18-month and 5-year follow-up. In all tests,  $\alpha$ -level smaller than 5% ( $p < 0.05$ ) was considered statistically significant.



## **5 RESULTS**

### **5.1 Long-term unilateral activity and bone mass, structure, and estimated strength**

Effects of long-term tennis and squash playing on mass, size and estimated strength of bone seemed to vary according to the measured bone site. In both male and female players, the cortical area of the shaft regions of the humerus was clearly enlarged and the bone seemed to have grown periosteally since the size of the marrow cavity was rather similar to that at the nonloaded site (Figure 7 and 8). In contrast, at the proximal humerus and radial shaft of the male players, besides on average 13% greater cortical and 17% greater total cross-sectional areas, the area of marrow cavity was 19% and 29% greater at the proximal humerus and radial shaft, respectively, compared to that at the nonloaded site (Figure 8). In all player groups as well as among the controls, the density of cortical bone was on average 1% to 2% higher in the less loaded arm. Compared to controls, in both genders of players, the bone strength indices were significantly higher at the loaded bone, especially at the humeral shaft (Figure 7).

At the distal radius, the variability in geometric variables between loaded and unloaded sites was large in all player groups. Thus, despite the rather large mean differences between players and their controls, the only significant between-group difference was seen in the side-to-side BMC difference in male players (10%) and in those female players (9%) who have started their playing during the growing years. In both female player groups, the side-to-side difference of trabecular density at the distal radius was also higher than that in the controls (Figure 9).

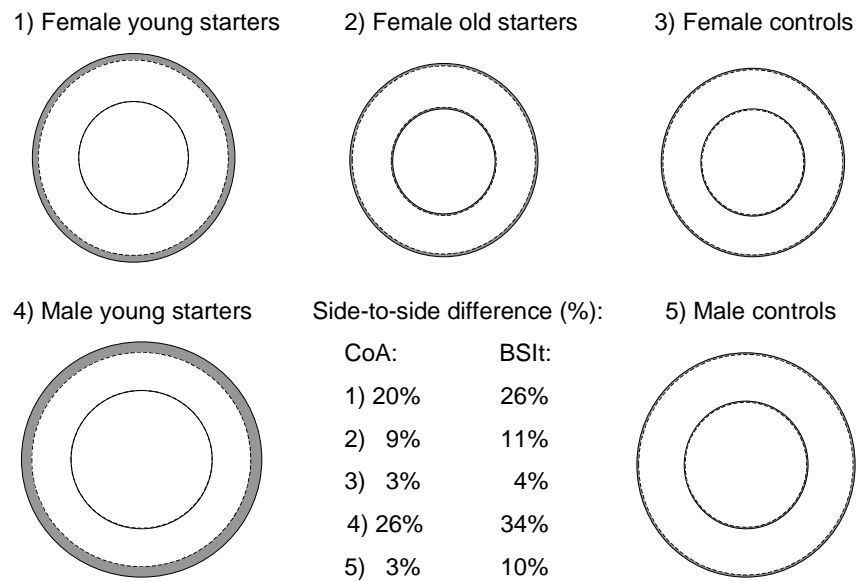


FIGURE 7 Illustration of the observed mean differences in the bone size, cortical area (CoA) and bone strength index (BSIt) of the humeral midshaft by displaying the cylindrical cross-sectional model of the playing arm over the nonplaying arm in female player groups, and male players, and their controls. Note the relative scale is actual.

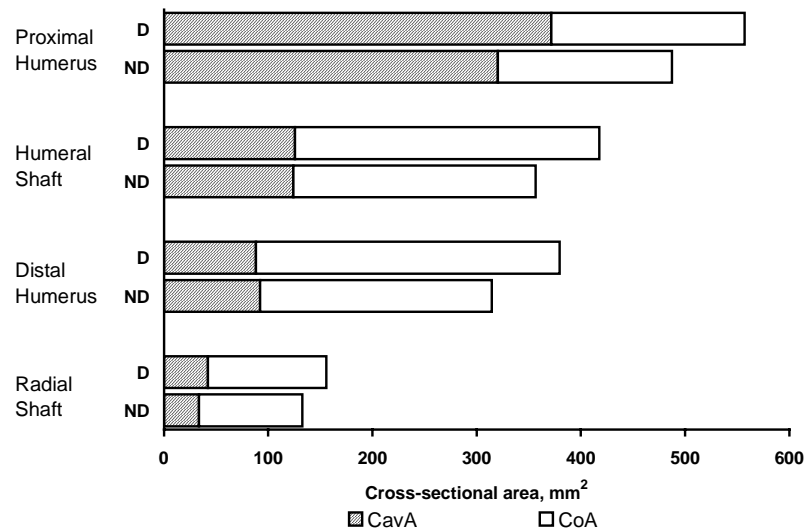


FIGURE 8 Mean side-to-side differences in the cross-sectional areas of the male players' marrow cavity (CavA) and cortex (CoA).

## 5.2 Effect of starting age of activity on bone mass, structure, and estimated strength

In female players, the long-term racquet-sports loading seemed to have induced periosteal bone growth at the loaded humerus, and compared to the side-to-side difference of total and cortical areas of the controls, this enlargement was noted in both groups of players despite the different starting age of the activity. However, the young starters' side-to-side differences in total and cortical CSAs were generally on average twice as large than those obtained in the old starters (Figures 6 and 8). The greatest benefit, in favor of the young starters was, however, seen in the bone strength index; compared to the controls, the net benefit in strength was 22% in young starters whereas the same in old starters was 7% only.

At the distal radius, the young starters' playing arm's BMC gain and increased trabecular density differed from those of the controls, while the old starters differed from the controls in the side-to-side trabecular density difference only (Figure 9). Interestingly, the mean side-to-side TrD difference tended to be higher in the old starters than young starters (Figure 9).

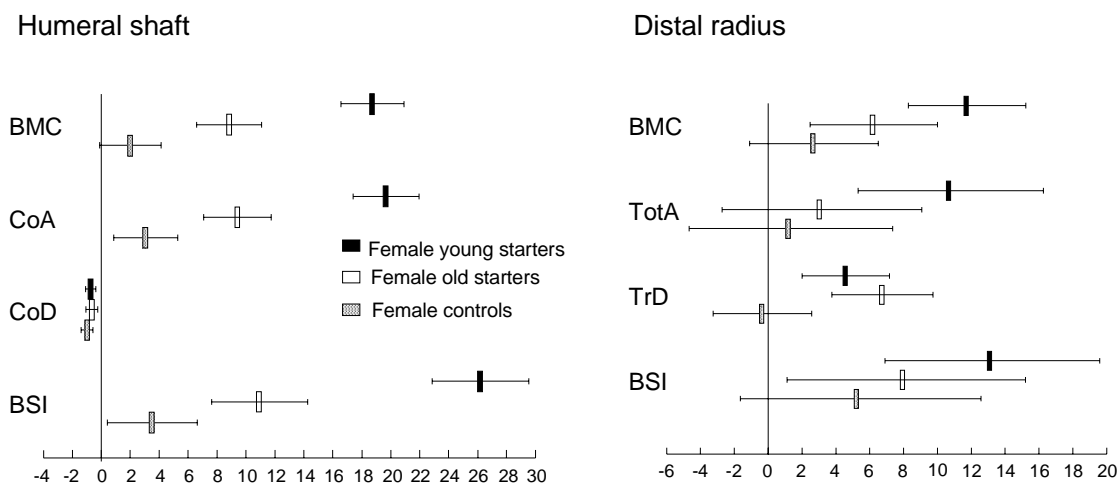


FIGURE 9 Female players' mean relative side-to-side differences and 95% confidence intervals at humeral shaft and distal radius, comparison between young and old starters and controls.

## 5.3 Maintenance of the exercise-induced bone gain

### 5.3.1 Maintenance after the competitive racquet-sport career

In general, the exercise-induced BMC gain was well maintained in male players at all measured bone sites, and in both female player groups (young and old starters) especially at shaft regions (Figure 10). Significant changes in BMC side-to-side difference were observed neither in male nor in female control groups.

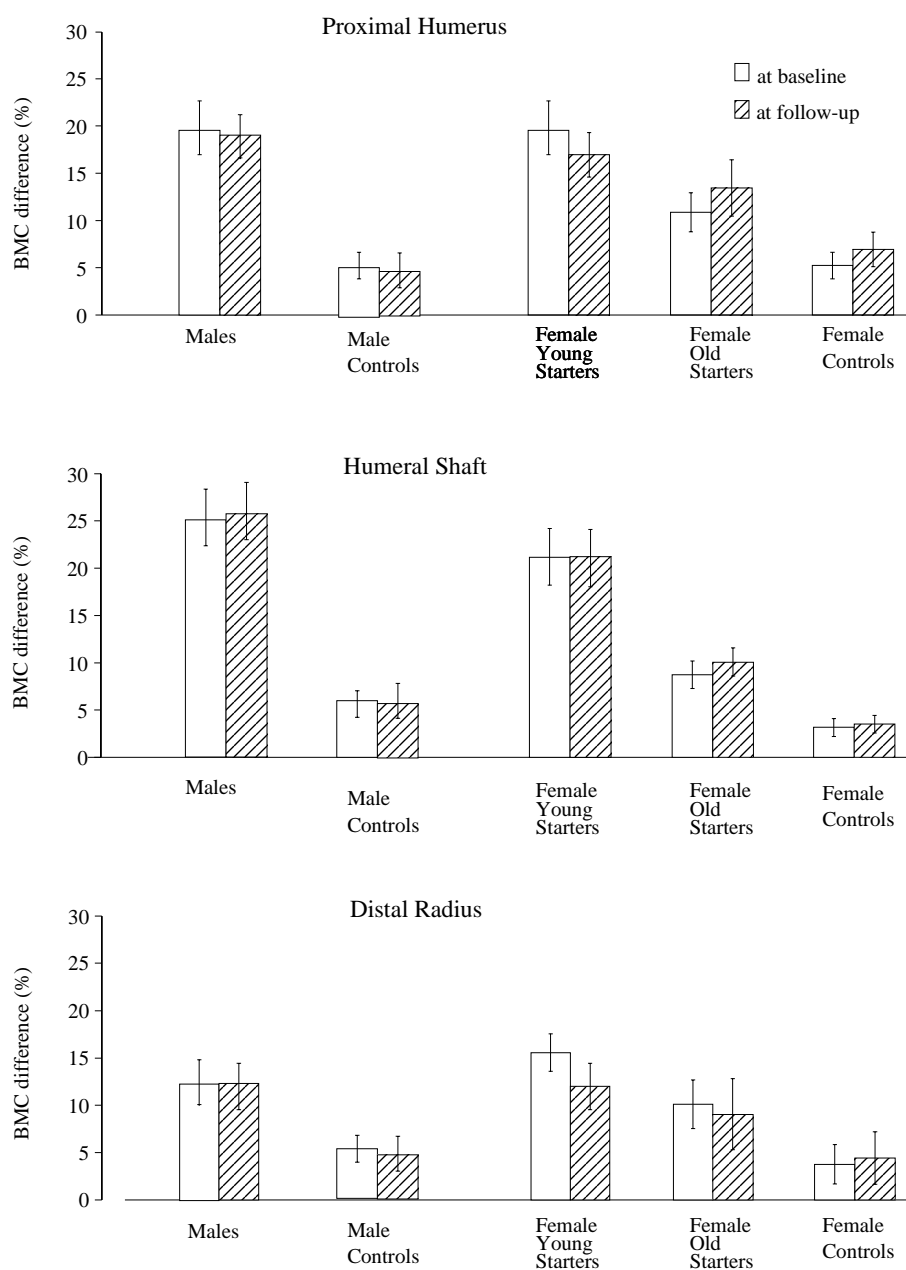


FIGURE 10 Male and female players mean side-to-side BMC differences and 95% confidence intervals at baseline and after 4-and 5-years follow-ups.

In female players, the young starters' BMC gain had decreased on average 3% at the proximal humerus and 2% at the distal radius due to a slight BMC increase (1.1%) in the non-playing arm and simultaneous BMC decrease (-1.1%) in the playing arm. Among the old starters, the BMC difference increased on average 2% at the proximal humerus and 1% at the humeral shaft. This slightly increased bone gain at the proximal humerus resulted from the decreased (-1.7%) BMC at the non-playing arm site while that of the playing arm remained at the same level (0.1%). Together these opposite changes in the relative bone gain at the proximal humerus in the young and old starters led to a 4% decrease in the mean relative side-to-side BMC difference between the young and old starters in the post-hoc analysis. Similar 4% decrease in the mean relative side-to-side BMC difference was obtained between the young starters and controls, since the change in the absolute BMC values of the proximal humeri were similar (eventhough statistically insignificant) with those of the old starters. At the humeral shaft or distal radius, there were no changes in bone gains between the groups.

#### *Players' side-to-side BMC difference in relation to change in training*

In both female and male player groups, there were no statistically significant associations between the changes in the training variables and the changes in the relative side-to-side BMC differences at any measured site. In female players, the individual side-to-side BMC changes were also analyzed separately among the ten players who had completely stopped their tennis or squash training at least one year before the follow-up measurement. However, no clear or systematically decreasing trend was found in these players' relative side-to-side BMC difference. This was also true in the male players who had stopped playing.

### **5.3.2 Maintenance after the high-impact activity interventions**

#### *Growing girls*

Twenty-month follow-up study with growing girls showed on average a 5% greater lumbar spine BMC accrual in those girls who had participated in the 9-month jumping intervention at the beginning of the 20-month follow-up compared to their controls (Figure 10). At the hip, the BMC gain difference was 2% in the femoral neck and 3% in the trochanter in favor of the trainees, but these differences were statistically insignificant.

In the performance variables, the only statistically significant between-groups difference at 20 months was found in the improvement of the long jump test, 6.3% in favor of the trainees. Neither did the improved leg extension strength nor the change in the shuttle run test differ between the former trainees and their controls at this 20-month follow-up.

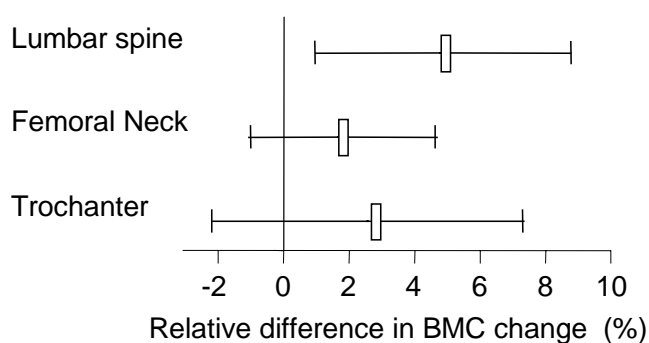


FIGURE 11 Comparisons of the 20-month BMC changes (mean %-difference, 95% confidence interval) between trainees and controls according to the regression analysis.

### *Premenopausal women*

Five-year follow-up measurements of premenopausal women revealed similar intergroup aBMD differences, in favor of the trainees, than those seen after the 18-month intervention. At the follow-up the statistically significant mean difference was found at lumbar spine (1.6%), femoral neck (1.9%), distal femur (2.4%), patella (1.6%), proximal tibia (2.8%), and calcaneus (1.9%) (Figure 11). No intergroup aBMD difference was seen at the trochanter and nonloaded distal radius after the 18-month intervention or at the 5-year follow-up.

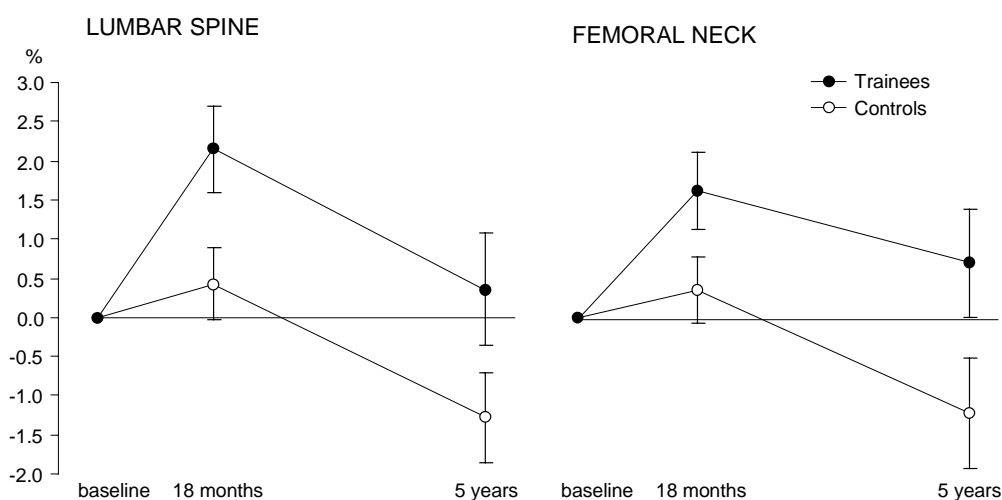


FIGURE 12 Mean percentage aBMD change at the lumbar spine and femoral neck during the 18-month training period and the subsequent three and half years of follow-up. Bars indicate the standard error of the mean (SEM).

In contrast to the maintained intergroup-difference in the exercise-induced aBMD gain, all significant 18-month improvements in the trainees' neuromuscular performance (isometric leg press, and vertical jump with and without additional 10% weight of the body mass) were lost at the 5-year follow-up.

## **6 DISCUSSION**

### **6.1 Exercise-induced changes in mass, structure, and estimated strength of bone**

Our pQCT-measurements showed that long-term racquet-sports playing was associated with an enlarged cortical area, especially in the shaft areas of the humerus and radius. In addition, the playing induced enlargement at the periosteal surface of the cortex leading to a greater total bone area at the loaded bone site. This was especially clear at the humeral shaft and distal humerus. These findings are in accordance with the earlier tennis studies using roentgenograms and CT, both of which observing cortical hypertrophy in the players' loaded humerus (Jones et al. 1977, Dalen et al. 1985). We also measured the distal radius, a bone site with substantial amount of trabecular bone. In the loaded arm, in addition to the somewhat enlarged bone size, trabecular density was increased in female players. In contrast, the density of cortical bone in the shaft regions was slightly but systematically greater in the less loaded site, including the nondominant arm of the controls. Thus, the current studies clearly demonstrated that bone mineral mass added to the dominant arm by tennis playing is mainly due to increased bone size, and not to volumetric density of the cortical compartment. This is especially true in the radial and humeral shafts. This was also observed in the earlier densitometric studies of tennis players that showed 10% to 40% greater BMC benefit at the loaded bone site (Montoye et al. 1980, Huddleston et al. 1980, Kannus et al. 1994, 1995, Haapasalo et al. 1998). Thus, the increased BMC and aBMD reported in many DXA studies may reflect mainly an enlarged bone size, not the greater volumetric density of the bone tissue. Therefore, the term 'increased bone mineral density' arising from the planar DXA measurements can be misleading.

When subjected to different types of loading the ability of bone to resist fracture depends on bone's structure and material properties, especially the distribution of the material (Forwood 2001). Bone can accommodate the same compressive load with material that is only half as strong if the cross-sectional

area is doubled (Currey 1984). Resistance to bending or torsion increases the further the material is situated away from the neutral axis of the load (Currey 2001, Martin 1991). The modeling response to mechanical loading may change bone geometry and lead to disproportionate increases in bending or torsional strength, independent of changes in material properties. This was reported in postmenopausal women whose distal radii adapted to increased loading. Cross-sectional area was enlarged and bone mineral from the trabecular bone compartment was, seemingly, transferred to the cortical shell without changes in densitometry-derived aBMD (Adami et al. 1999). Respectively, improved mechanical strength was reported in rats' loaded proximal femur without any concomitant change in BMC (Järvinen et al. 1998). For these reasons, reevaluation of the results of numerous longitudinal exercise studies that showed no or only mild-to-moderate exercise-induced benefit in BMC and aBMD has been suggested (Järvinen et al. 1999, Forwood 2001). Simply speaking, the effects of mechanical loading on bone integrity and strength could potentially be better than what has been reported for BMC or aBMD measurements alone.

Thus, in study II, we assessed this theory by comparing the DXA-derived side-to-side aBMD difference to that of the BSI. BSI is currently considered the most reasonable noninvasive surrogate of bone strength, especially at the long bone shaft. In other words, does aBMD provide the same estimation of exercise-induced strength gain as does BSI? Or does it underestimate the effects of long-term racquet-sports loading on bone? In the shaft area, mean relative exercise-induced bone benefit was on average 36% lower if estimated by aBMD than by BSI. The same was also clearly seen in individual players. For example, in one player, side-to-side aBMD difference at the humeral shaft was 33%, as compared to 44% for BSI. In other players, these values were 23% and 37%, and 15% and 21%, respectively. These, on average, 10% systematically lower values for aBMD as a surrogate for bone strength reflect the fact that aBMD does not specifically assess the loading-induced cross-sectional bone growth at the shaft area. This was especially obvious in the humeral shaft of the young starters. This suggests that exercise-induced (or growth-related) changes in bone dimensions must be evaluated with a method that detects bone enlargement in three dimensions. However, to assess which of these two surrogates are superior in terms of bone strength, the comparison must be made with the real golden standard, mechanical testing.

## **6.2 Effect of starting age of activity on exercise-induced changes in bone mass and structure**

Animal studies provide indisputable evidence that growing bone has better capacity to increase bone mass than mature bone and, moreover, immature bone seems to use different strategies for adaptation. Young bone has greater



potential for periosteal expansion than aging bone, while mature bone may preferentially increase bone mass by increasing osteonal mean wall thickness (Forwood & Burr 1993, Forwood 1998). The results of our female player study (II) support this and showed a side-to-side difference in cortical area of the humeral shaft that was more than two times greater in the young starters versus old starters. At the distal radius, the group differences were not as distinct, although in the young starters the size of the loaded radius was significantly greater than the unloaded radius. In the old starters, however, no difference was observed for total bone area, but cortical wall thickness was greater at the loaded site. This might represent corticalization of subcortical trabecular tissue.

Thus, at the long bone ends, bone's structural response to loading may differ from that at the bone shaft due to greater proportion of trabecular bone and exposure to different types of loading. After cessation of growth, the joint and epiphyseal region are unlikely to enlarge in size, thus, while increased trabecular density and cortical thickness, and redistribution of bone mineral may be mechanisms that structure increases bone strength (Martin 1991). Ashizawa et al. (1999) measured the distal radius with pQCT and revealed that three players, who had started playing not until the age of 16 had increased trabecular density, not increased radial cross-sectional area. In players who had started playing when younger, the reverse was reported. Our results gave faint support to these findings as we saw a tendency for greater cortical wall thickness and trabecular density in the old starters than young starters compared with controls. However, this difference, in favor of the old starters, was not statistically significant.

Loading-induced over 20% greater bone CSA in female and male young starters. If these adaptations persist into adulthood they could significantly help maintain bone integrity in later life. Periosteal expansion, although in lesser amounts, has been related to aging at the femoral neck and shaft (Cheng et al. 1995, Beck et al. 2000) and vertebral body (Mosekilde & Mosekilde 1990). This phenomenon may reflect an effective compensatory mechanism against the loss of bone mineral at the trabecular and endocortical bone sites (Carter et al. 1996). Subperiosteal expansion of bone with age is thought to be in direct response to increased peak strains on that surface and the net loss of bone from the endocortical surface (Carter et al. 1996). In contrast, a recent side-to-side pQCT comparison with tennis players who started playing after age of 30 years, showed a smaller periosteal and endocortical areas at the loaded radius compared to that at the nonloaded site (Nara-Ashizawa et al. 2002). This suggests that mechanical loading may suppress the age-related enlargement at both periosteal and cortical-endosteal envelopes (Nara-Ashizawa et al. 2002). Unfortunately, there was no control group in this study. Thus, it was difficult to assess whether the side-to-side difference was directly caused by recreational unilateral loading. On the other hand, larger bones and a mechanically more competent structure in the radial and tibial shafts were related to physical activity in postmenopausal women (Uusi-Rasi et al. 2002a).

Subperiosteal expansion does not have to be large to contribute significantly to bone strength. Beck et al. (2000) provided an elegant illustration of this phenomenon. Expanding a 2-cm wide endocortical diameter of a 3-cm wide tubular bone by 10% (2-mm) will reduce aBMD by about 16%. To maintain the section modulus unchanged, only a 0.83-mm simultaneous increase in the subperiosteal diameter would be required, and although this results in a net loss of about 9% in aBMD there would be no real change in bending or torsional strength (Beck et al. 2000). Similarly, in our female and male players the mean increase in bone at the periosteal surface of the loaded humerus (assuming the bone cross-section is cylinder) was 0.83 mm in men, 0.58 mm in the young female starters, and 0.24 mm in the old female starters. However, these small increases led to 34%, 26% and 11% greater section modulus in the playing arms of these players, respectively.

The above noted findings are important: they provide evidence that mechanical loading has pronounced effects on growing bone, not only by increasing mineral accrual but also by improving bone geometry. Thus, our results give some support to the earlier densitometry-derived findings (Haapasalo et al. 1996, Bradney et al. 1998, Marcus 1998). However, the loading-induced enlargements in total and cortical CSA we observed are somewhat different than the earlier DXA-derived alterations in the bone dimensions of the humerus. The estimated increase in mean cortical wall thickness was greater when data were obtained by DXA. Conversely, humeral width increased less, on average, compared with changes by pQCT (Haapasalo et al. 1996). From DXA data, bone width is calculated by dividing the projectional area by the length of the ROI (Sievänen et al. 1994). The small, subperiosteal enlargement is not visible by DXA as DXA derived area is perpendicular to the measured projection of the given bone (Sievänen et al. 1996). Thus, estimations of bones' outer dimensions may be inaccurate.

In general, it is less complicated to assess bone characteristics at the shaft than at the bone ends where geometry and structure are more complex (Sievänen et al. 1996, 1998). Similarly, the adaptive response of whole bone architecture to mechanical loading is also very complex (Mosley and Lanyon 1998, Forwood 2001). An experimental study by Mosley and Lanyon (1998) adjusted ongoing cell activities which stimulated coordinated and site-specific changes in the entire bone modeling patterns, not just changes in the rate of bone deposition and resorption responses. Hereby pointing that careful consideration must be given when sample site is selected since single localized samples may not represent the global response of the bone to mechanical load. In some cases results from a localized site may be entirely misleading as a representation of whole bone response (Mosley and Lanyon 1998). Currently, it is impossible to evaluate whole bone geometry and integrity at different parts of the skeleton in a clinical setting. Hopefully safe measurement techniques that allow this will be developed in the near future.

Various approaches have been utilized to estimate characteristic of bone geometry and mechanical properties, as well as its mineral apparent density

(BMAD,  $\text{g}/\text{cm}^3$ ) from DXA measures of BMC and aBMD (Sievänen et al. 1996, Carter et al. 1992). At the long bone ends, it has been suggested that BMAD is the appropriate parameter to assess mechanical competence in compressive loading. The adjustment for site-specific estimate of bone size can alleviate the effects of variation in regional bone size and shape during skeletal growth (Katzman et al. 1991, Kröger et al. 1993). BMAD has not, however, achieved popular use. On the other hand, incorporating geometric parameters related to bone strength may provide greater clinical validity and reliability to estimate bone strength than BMC or aBMD alone (Beck et al. 1990, Sievänen et al. 1996, Carter et al. 1996). Together with age and BMI, the Hip Strength Analysis (HSA) provided a significantly better prediction of hip fracture than aBMD of the femoral neck alone (Crabtree et al. 2002). HSA may prove to be a reasonable adaptation of densitometry data for clinical practice. Recently this method was utilized in the field of physical activity and pediatric bone research (Petit et al. 2002). The authors compared 7-month change in bone structural properties in pre- and early-pubertal girls randomized to exercise intervention or control groups. They showed that the increased aBMD at the femoral neck and trochanteric area in the more mature girls was a function of increased bone CSA and reduced endosteal expansion, which also improved section modulus at the femoral neck (Petit et al. 2002). However, in order to assess structural parameters of both bone and muscle MRI seems to be the most promising technique at the moment (Heinonen et al. 2001b)

Heightened adaptation to mechanical loading observed in growing, compared with adult, bone may be due to the fact that during longitudinal growth bone is added in substantial amounts to both the inner (endosteal) and outer (periosteal) surfaces of bone. This is the only time throughout life when this occurs and endosteal accumulation diminishes thereafter (Parfitt 1994). In experimental studies, growing bone responded to exercise by adding significant amounts of new bone at periosteal, endocortical and trabecular sites. No exercise-induced endocortical bone accumulation was observed in mature bone (Forwood & Burr 1993). Although our pQCT-studies were cross-sectional comparisons, and thus the cause-effect relationships cannot be completely verified, our findings do not provide evidence for the exercise-induced endocortical bone accrual in young or old starters. The response to an imposed load (or lack of it) may well depend on the bone site measured, as well as the loads and strains prevalent in the different bones and their parts. However, the absence of the smaller marrow cavity at the loaded humeral shaft of the young starters is discordant with findings of exercise intervention-induced endosteal contraction or reduced endosteal expansion at the femoral shaft (Bradney et al. 1998) and neck (Petit et al. 2002). These differences may be due to a number of factors; 1) inability of planar measurements to assess bone structure adequately; 2) potential errors in repositioning of the subject, especially when measuring the femoral neck (Sievänen et al. 1994); 3) age or maturity differences between cohorts; 4) differences in study design.

Substantial increases in cortical area, cortical wall thickness, and section modulus of bone have recently been demonstrated in triple jumpers and weightlifters (compared to their age-, weight- and height matched controls) at the lower and upper extremities (Heinonen et al. 2001a, 2002). It must be noted, that neither selection bias nor other confounding factors can be thoroughly excluded from the cross-sectional comparisons of athletes and their controls. In this respect comparison between loaded and unloaded arms of racquet sports players and their controls provides a more reliable study design. However, the exercise-induced adaptations at the humerus and radius cannot be generalized to other bone sites, especially to the clinically important proximal femur and spine. Exercise-induced adaptations are site-specific even within adjacent parts of the same bone. Therefore, the future prospective, randomized exercise trials in children, adolescents, and adults, should assess a wide variety of anatomical sites with a precise and accurate three-dimensional imaging technique.

### **6.3 Maintenance of the exercise-induced bone gain in retired racquet-sports players**

Retrospective cross-sectional studies on former athletes and their controls have given preliminary evidence that at least a part of the in-adolescence-obtained, exercise-induced bone gain may persist despite decreased physical activity (Karlsson et al. 1995 and 1996, Lindholm et al. 1995, Kirchner et al. 1996, Khan et al. 1996 and 1998, Bass et al. 1998, Magnusson et al. 2001). Our 4- and 5-year prospective follow-up studies of male and female racquet sports players showed that a positive side-to-side BMC difference between the playing and nonplaying extremity remained at the follow-up. The mean training frequency and hours of training were clearly decreased during the follow-up period, thus, supporting the results of the above noted cross-sectional studies.

Additionally, exercise-induced bone gain was maintained in both groups of female players regardless of the clearly different starting age of activity. Maintenance was also unrelated to the magnitude of the exercise-induced bone gain. Thus, our results did not directly support the notion that exercise-induced bone gain obtained in adolescence may withstand the effects of decreased training better than bone gain obtained in adulthood (Parfitt 1994). At the proximal humerus, the female old starters even slightly increased their relative side-to-side BMC difference compared to a decrease in side-to-side BMC difference among the young starters. These changes were a result of either a BMC increase in the nonplaying arm with a concomitant increase in the playing arm (young starters) or a decrease in the non-playing arm with no change in the playing arm (old starters). However, since all these absolute BMC changes were within the 1-2% precision error of the measurement (Sievänen et al. 1994), they should be interpreted with caution. Both the individual changes of the completely detrained ten female players and the mean changes in the young

and old starters' side-to-side BMC difference seemed to be greater at the bone sites that contained more trabecular bone (proximal humerus and distal radius) than cortical bone (humeral shaft). This was especially clear among the young starters whose side-to-side difference decreased at the proximal humerus and distal radius but remained unchanged at the humeral shaft. It may well be that decreased loading has a greater influence on trabecular bone sites where high surface-to-volume ratio makes the bone more susceptible to rapid mineral turnover (Ruff and Hayes 1982, Parfit 1994, Forwood & Burr 1993). Further, by measuring BMC alone it is impossible to resolve the changes in bone mineral distribution and structure within the given bone section. Thus, subsequent influences of detraining on these important surrogates of bone strength are not discernible.

Some animal experimentals suggest that exercise-induced bone is maintained during a short detraining period (Kiuchi et al. 1998, Silberman et al. 1991, Biewener et al. 1996, Singh et al. 2002). In contrast, there are a few animal (Yeh and Aloia 1990, Kannus et al. 1996, Iwamoto et al. 2001) and human studies (Dalsky et al. 1989, Vuori et al. 1994, Winters et al. 2000, Iwamoto et al. 2001) showing that after even a short detraining period, exercise-induced aBMD benefit at trabecular regions returns toward pretraining values. This suggests that long-term benefits can be retained with continuing exercise only. The current studies suggest that the amount of training needed to maintain exercise-induced bone alterations is less than that needed to accrue more bone. To support this, premenopausal women who attended aerobic classes approximately twice a week maintained exercise-induced bone gain after cessation of an intense jumping training (Heinonen et al. 1998).

One limitation of our athlete follow-up studies is that greater changes (reductions) in players' side-to-side BMC difference may occur after 5 years of reduced participation in sport. That is, in studies III and IV, most of the players may still have been active enough to maintain their exercise-induced bone gain. The decreased, but still regularly performed tennis or squash training may have produced sufficient stimulus to maintain the training-induced bone gain at the measured sites. Consequently, there is a clear need for longer follow-up studies so that a greater number of players may stop playing completely. Complete cessation of training may result to different alterations in the exercise-induced bone gain at the shaft region compared to that at the proximal and distal parts of the bones. Assessment of the structural properties of bone and changes in these surrogates of strength enable a better understanding of the magnitude, quality, and longevity of improved bone integrity produced by mechanical loading in growing and mature bone.

## 6.4 Maintenance of the exercise intervention-induced bone benefit

At 20 month follow-up, study V showed a 5 % greater lumbar spine BMC accrual in pre- and postmenarcheal girls who participated in the 9-month jumping intervention compared to controls. At proximal femur sites, BMC gain difference was 2% at the femoral neck and 3% at the trochanter in favor of the trainees, but these differences were not statistically significant. Improved explosive muscle strength was also maintained in trainees at follow-up. According to current literature search, no other reports evaluate the effects of previous exercise intervention on bone mineral accrual in growing girls.

The greatest challenge in study V was controlling for the primary factors that determine bone accrual during growth prior to estimating the effects of previous exercise. The improved measures of physical performance during, and a year after, the intervention supported the effectiveness of the jumping training for the development of strength and power in growing girls. Furthermore, our findings provide further support to that jumping training can be an effective and feasible means to strengthen both bones and muscles in this age group (McKay et al. 2000, Fuchs et al. 2001, MacKelvie et al. 2001, 2002). On the other hand, it may be that the trainees' other physical activities during the follow-up were strenuous enough to maintain muscle strength and, thus, the additional bone obtained. There was no difference in improvement of leg extension strength between trainees and controls after changes in the other growth-related parameters (i.e, age at baseline, increases in height and weight, and pubertal maturation) were taken into account. This might suggest that the isometric leg press is a less valid test to determine the effectiveness of a dynamic jumping intervention and its withdrawal than the standing long-jump (Kannus et al. 1996b). On the other hand, to enable between-group comparisons in both bone gain and improvement in the performance variables, same covariates were used in the statistical model. The strongest predictors of bone changes (increases in height and weight, and pubertal development) presumably explain the majority of the improvement in physical performance tests. Comparison between trainees and controls might have been different if covariates were selected to primarily explain changes in physical performance.

Limitations of study V arise from the observational nature of the follow-up. First, although the mean background characteristics and bone variables between both groups were similar at baseline, there was a noteworthy interindividual variation in growth and maturation. Thus, the direct comparison between the original pre- and postmenarcheal training and control groups was impossible to perform and therefore the regression analysis model was created. Second, at the postintervention phase, we were able to describe the changes in the girls' physical activity with relatively general terms only, and therefore, it was difficult to assess the exact effect of the various follow-up activities on bone changes by time. Seventeen girls from the training group

wanted to continue the step-aerobic training with additional jumps at a local gym. However, their final BMC accrual did not differ from that of the other trainees. It could be that their bones had already accustomed to the type, frequency, intensity, and directions of the nonprogressively continued jump training while a subsequent extra BMC benefit would have required more strenuous and frequent, and perhaps different type of, activity than was done before. Again, the amount of training needed to maintain the exercise-induced bone gain might be less than that needed to achieve the additional bone.

The current literature suggests that exercise-induced bone benefits start to disappear after cessation of training, particularly if the bone benefit has been obtained after the skeletal maturity (Dalsky et al. 1988, Karlsson et al. 2000, Iwamoto et al. 2000, Winter and Snow 2000). However, in the study VI with premenopausal women, the training-induced aBMD difference between the former trainees and controls was well maintained for a detraining period of three and half years, although the training-induced intergroup differences in physical performance tests were lost at the same period of follow-up. The study thus suggests that the high-impact activity-induced bone benefit can be maintained with ordinary, low-impact type of activities, such as walking, cycling, and low-intensity weight-training classes. This is an important criterion when considering the feasibility and long-term utility of training interventions in adult women. However, it may also be that the impact-training induced improvements in neuromuscular performance can be maintained with impact-type (plyometric) training only. The maintenance of neuromuscular performance, especially the properties related to muscle strength, motor control, agility and balance, is however, of great importance since good neuromuscular function is directly related to reduction in the risk of falling (Kannus 1999, Carter et al. 2000, Kannus and Khan 2001).

On the other hand, if bone benefits can be maintained with less strenuous training, risks associated with vigorous exercise can be avoided. High intensity and high volume endurance training has been associated with bone loss in both the axial and appendicular skeleton (Drinkwater 1996, Snow 1996). Vigorous training and restricted energy and nutrient intake related to eating disorders may also induce oligo- and amenorrhea, and deteriorate bone health (Yeager et al. 1993, Drinkwater 1996, Snow 1996, Khan et al. 2002). On the other hand, activities that deliver high loads may offset the negative bone effects of low reproductive hormones (Snow 1996). Interestingly, estrogen status may also be related to the effectiveness of the exercise-induced bone gain and the maintenance of the bone benefit. In postmenopausal women, weight-bearing exercise together with hormone replacement therapy (HRT) showed an additive effect on aBMD at the lumbar spine and proximal femur and the increased aBMD was preserved during the 6-month follow-up only in those individuals on HRT (Kohrt et al. 1995, 1998).

The limitation of study VI was its observational nature after the 18-month randomized controlled exercise trial. This applies particularly to the evaluation of the subjects' physical activities and their changes during the follow-up.

Although all subjects answered the questions about the type, frequency, intensity, and duration of the activities they were engaged in during the post-intervention follow-up, only few had performed these activities so regularly that they could give exact answers. On the other hand, in general the post-intervention activity levels were moderate only, and the former trainees and controls had practised very similar types of low-impact activities after the intervention so that the observed between-group aBMD differences at 5 years were likely attributable to true maintenance of the 18-month training-induced aBMD gain. In addition, only three former trainees continued step-aerobic classes throughout the 3.5-year follow-up period and these step-aerobic classes contained mainly stepping on and off step benches without additional impacts from jumps, such as was progressively done during the 18-month intervention (Heinonen et al. 1996). Also, the disappearance of the between-group difference in the leg extension strength and power during the post-intervention phase speaks strongly for true detraining of the former trainees (with respect to jumping and other high-impact activities) and thus true maintenance of the jumping-induced bone gain.

The earlier detraining studies with pre- and postmenopausal women have suggested that the benefits of exercise may become lost after the end of the intervention (Dalsky et al. 1988, Winters and Snow 2000, Iwamoto et al. 2000). In two of these studies (Dalsky et al. 1988, Iwamoto et al. 2000), however, the number of subjects was rather small and only lumbar spine aBMD was measured. In the recent study with premenopausal women spine, proximal femur and total body aBMD changes during the 6-month detraining period were evaluated using a within-subjects design for detrainees and controls separately, which raises a question, whether the interpretation of the results would have been different if the detraining effects had been analyzed similarly as the training effects were, i.e. by between - groups analysis of covariance (Winters and Snow 2000). In study VI, both trainees and controls showed subsequent aBMD loss in many of the bone sites although the intergroup difference (i.e., the exercise-induced aBMD benefit) still existed at the 5-year follow-up.

Most of the subjects in our follow-up studies could be categorized as moderately physically active, although in a reduced level compared with the time when they were either competing or participated in the intervention classes. It may well be that the exercise-induced bone benefit could not be maintained if these subjects had become completely sedentary. An important concern of any intervention treatment is thus the maintenance of the produced benefit: in other words, the Achilles heel of exercise can well be in its cessation (Sievänen et al. 2000b, Karlsson and Seeman 2000, Nelson and Bouxsein 2001, Kontulainen et al. 2001, Karlsson 2001, Seeman 2001). However, according to current data, complete cessation of all physical activity may be more rare (especially among athletes) than transition to a reduced level and less intense types of activity. And, this lower level of activity appeared to be enough to maintain the skeletal benefits obtained during the earlier strenuous training.



Nevertheless, one has to keep in mind that there can be some bias in the results of exercise trials where subjects volunteered. Volunteers may have some properties, characteristics, or a situation that may predispose them to volunteer for the study, and thus, enable them to obtain the benefits and even to maintain them. However, if further studies confirm our promising evidence that the benefits from a period of high-impact activity can be maintained even for years with more ordinary physical activity only, these results can make strenuous training periods more feasible and motivating and thus, encourage people to participate in training.

Finally, a fundamental future question is what will happen to these favourable 5-year results when the subjects will enter into menopause, a period of rapid general bone loss, and moreover, can the exercise-induced benefit be maintained, and eventually can it prevent fractures in old age. Thus, a further follow-up of our subjects and other randomized controlled trials examining the effect of exercise, calcium, vitamin D, or bone-specific drugs are warranted to show the long-term effects of such an intervention. Cross-sectional comparisons cannot provide the basis from which to truly estimate secular trends in bone mass accrual or loss or other important aspects of bone integrity (Karlsson et al. 2000, 2001, Sievänen et al. 2000b, Lorentzon et al. 2000, Donaldson et al. 2001, Seeman 2002).

An optimal study design to assess whether a reduced level of exercise maintains the exercise-induced bone benefits obtained during growth, and eventually reduces the risk of fracture, would be a randomized trial with a life-long follow-up. However, such trials may never be done and, thus, carefully performed prospective cohort follow-ups are also pertinent to receive the best possible answer to this important question. The evidence presented from the prospective follow-up studies of retired racquet sports players and the high-impact activity interventions in girls and premenopausal women is consistent. These studies show that a loading-induced bone benefit is maintained at least during the subsequent periods of reduced training. Furthermore, our findings support the epidemiological studies that provide evidence that intense physical activity during the growing years, followed by moderate activity in adulthood, may decrease the risk of fracture later in life (Joakimsen et al. 1997, Gregg et al. 1998, 2000, Kujala et al. 2000, Ling et al. 2000). Moreover, of all the strategies to prevent fracture, regular physical activity is the only one that provides considerable other health-related benefits (The Surgeon General Report 1996, Dose-response issues concerning physical activity and health 2001). For these reasons, the current view is that regular exercise should be strongly recommended for both younger and older people.

## 7 SUMMARY AND CONCLUSIONS

The primary findings and conclusions of the present series of studies can be summarised as follows:

- I Studies I and II demonstrated that long-term racquet sports training had increased bone mineral mass and built a stronger bone structure at the loaded arm's proximal humerus, humeral shaft, distal humerus, and radial shaft mainly by increasing the bone size, not the volumetric density of the cortical bone. In fact, the density of the cortical bone in these bone regions was slightly but systematically greater in the less-loaded bone site in players, as well as in the nondominant arm of the controls. The greater bone size at these loaded bone sites was due to enlargement of the periosteal surface of the cortex. At the male players' proximal humerus and radial shaft, the area of marrow cavity was also greater at the loaded bone site. At the distal radius, besides the somewhat enlarged bone size, the trabecular density at the loaded bone site was increased in the female players. To conclude, playing long-term racquet sports had increased bone mass in the loaded upper arm mainly via periosteal enlargement of the cortex, and thereby built a stronger structure of bone at the loaded site.
  
- II In both of the female player groups the structural adaptation to the long-term loading was achieved through the above noted periosteal enlargement of the bone cortex at the humeral shaft. However, this adaptation was two times better in those players who have started playing before or at puberty rather than after it. Comparison of this exercise-induced benefit in terms of bone strength between the young and old starters was even greater than the gain in bone size. Exercise-induced enlargement in bone size was not so clear at the distal radius. Indeed study II suggested that at the ends of long bone the apparent trabecular density might increase in response to long-term loading. These results emphasize the importance of exercise during the growing

years - not only to enhance the accrual of the peak bone mass but especially to increase bone size and thus, improve bone strength, a key component of fracture prevention.

- III Studies III and IV examined whether or not the bone benefit achieved by playing racquet sports is maintained despite 4 and 5 years of reduced training. These studies indicated that the exercise-induced bone gain was well maintained in male players and in both groups of female players regardless of their clearly different starting age of activity and the magnitude of the exercise-induced bone gain. Thus, the results did not support the notion that the exercise-induced bone gain that is obtained during the growth may better withstand the effects of decreased training than the bone gain obtained later in adulthood.
- IV Consistent with the above noted maintenance of the exercise-induced benefit after reduced racquet-sports training, study V showed that the positive effect of 9-month jumping intervention on bone accrual in growing girls was maintained at the lumbar spine a year after the end of the intervention. At the hip, bone mineral accrual was also in favor of the former trainees but these differences were statistically insignificant. The difference between the former trainees and their controls in the improvement of the explosive type of muscle strength was noted, in favor of the trainees, during the follow-up. Finally, the 5-year follow-up study (VI) of the premenopausal women showed good maintenance of the training-induced bone benefit in the former trainees compared to their controls during a detraining period of three and half years. In contrast, the post-intervention differences in physical performance tests between the groups, in favor of the trainees, were lost during the same period of detraining. Thus, study VI suggested that the high-impact activity-induced bone benefit in premenopausal women could be maintained with ordinary, low-impact type of activities only. This is an important consideration when evaluating the feasibility and long-term utility of training interventions among adult women.

## 8 YHTEENVETO

Tutkimuksen kahden ensimmäisen osatyön tarkoitus oli selvittää pitkäaikaisen kuormituksen vaikutuksia luun rakenteeseen, luumassaan ja - tiheyteen sekä arvioituun luun vahvuuteen. Tennispelaajien käsien välisiä luostopuolieroja tutkittiin perifeeristä tietokonetomografialla (pQCT) olkaluun yläosasta, varresta ja alaosasta, sekä värttinäluun varresta ja ranteesta. Pelikäden suurempi mineraalimassa oli seurausta isommasta luusta, kun taas kuoriluun tiheys oli järjestelmällisesti hieman matalampi kuormitetumman käden luussa, myös vertailuhenkilöillä. Suurentunut koko kuormitetussa luussa oli seurausta luun ulkomittojen laajentumisesta (periosteaalinen kasvu). Miespelaajilla olkaluun yläosassa ja värttinäluun varressa myös ydinontelon pinta-ala oli suurempi kuormitetussa kädessä. Ranteessa peliharjoittelu oli tuottanut hienoisen luun koon suurentumisen lisäksi myös jonkin verran tiheämmän hohkaluun.

Naispelaajilla arvioitiin myös harjoittelun alkamisiän vaikutusta luun rakenteeseen ja vahvuuteen. Sekä kasvuiässä että aikuisena pelaamisen aloittaneilla vasteet olkaluun varressa olivat samankaltaisia, mutta muutosten suuruudessa oli selvä ero. Kasvuiässä pelaamisen aloittaneilla puoliero luun lujuusindeksissä oli verrokkeihin nähden 22% suurempi kun taas aikuisena aloittaneisiin nähden tämä ero oli 14%. Liikunnan luuta vahvistava vaikutus on siis selkeästi parempi kasvuiässä kuin sen jälkeen.

Neljässä seuraavassa osatyössä selvitettiin liikunnan tuottaman luulisän pysyvyyttä harjoittelun vähentyessä tai liikunnan lopettamisen jälkeen. Neljän ja viiden vuoden seurannat mies- ja naispelaajilla osoittivat, että huolimatta selvästä harjoittelumäärän laskusta, keskimääräinen pelikäden luulisä oli säilynyt ennallaan. Harjoittelun aloitusiällä ei myöskään ollut vaikutusta luulisän pysyvyyteen. Luuliikuntainterventioiden jälkeisten seurantojen tulokset olivat samansuuntaisia. Tyttöjen seurannassa tutkittiin eroaako luuston mineraalimäärän kasvu yhdeksän kuukauden hyppelyharjoitteluun osallistuneilla tytöillä vertailutyttöihin nähden vielä vuoden kuluttua intervention päättymisestä. Tutkimus osoitti, että luuston mineraalimäärän muutoksesta suurin osa selittyy kasvulla, ja että kuormituksen tuoma luulisä ilmeni lannerangassa vielä vuosi intervention päättymisestä. Vastaavasti luuliikunnan avulla saavutettu etu luun

mineraalitiheydessä verrokkeihin nähden oli säilynyt vielä kolme ja puoli vuotta harjoittelun lopettamisen jälkeen premenopausaalisilla naisilla.

Kaikki tutkimuksen tulokset lisäävät näyttöä, että fyysisestä kuormituksesta on pitkäaikaista hyötyä luustolle. Siksi liikuntaa voi suositella osteoporoosin ja siihen liittyvien murtumien ehkäisyyn.

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