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148

Timo Rantalainen

Neuromuscular Function and Bone Geometry and Strength in Aging

JYVÄSKYLÄN YLIOPISTO

STUDIES IN SPORT, PHYSICAL EDUCATION AND HEALTH 148

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UNIVERSITY OF JYVÄSKYLÄ

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ABSTRACT

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Finnish summary

Osteoporosis, falls and ensuing bone fractures cause individual suffering and economical burden. Pharmacological interventions are not cost effective for preventing these osteoporosis and aging related bone fractures, and therefore non-pharmacological interventions, such as exercise should be considered. The purpose of this thesis was to study the associations between body mass, neuromuscular performance (impulse and power in different types of jumps) and skeletal rigidity in both genders and in young and elderly subjects. The results of the studies suggest that tibial rigidity is related to maximal neuromuscular performance in young and elderly men and women. The association between bone rigidity and neuromuscular performance seemed to be moderate, but site and loading specific. Furthermore, neuromuscular performance adds to the predictive power of regression models beyond that of body mass. The difference in the bone rigidity to loading ratio between young and elderly individuals is bigger than one might expect from the delay in bone adaptation alone, indicating changes in skeletal mehcanosensitivity. However, even in the elderly, habitual explosive exercise seems to be associated with more rigid bones. Individual determinants of neuromuscular performance, such as specific tension, may contribute to increasing skeletal integrity and can be positively manipulated with exercises, which have also shown to be effective in fall prevention.

Keywords: Bone, neuromuscular performance, aging, predictors of bone strength, bone geometry

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I have always looked up to my dad and thought, I wish I could do as well as he has. One day, when I was in the elementary school, I found my dad's stamp, where it said Markku Rantalainen, Lääketieteen lisenssiaatti (licenciate of Medicine) and I asked my dad: "Daddy, what does licenciate mean?" "Well, there are four kinds of certificates you can acquire from the university: the Bachelor's, Master's, Licenciate's and Doctor's" my dad responded. At that point in time, I remember myself thinking, this is my chance to not only match but actually even surpass my father's accomplishments. Since that time I have matured a little and do not feel the need to compete with my father's accomplishments any more (that would not be a fair competition in any case, since my dad is simply awesome in every aspect of life that I care of). In any case, that was the beginning of my interest in academia. Eventually, in the fall of 2004 I started working on my master's thesis and got the priviledge to be one of Professor Paavo Komi's last master (and subsequently doctoral) students. Prof. Komi was really an intimidating and distant figure for me but after sitting through some seminars I managed to gather my courage and asked if I could be accepted as a doctoral student. I remember the answer as it were yesterday: "One does not become a doctoral student simply by spending time on the gluteus". That didn't sound too promising, to say the least. Subsequently, I did become a doctoral student. I wish to express my deepest gratitude to Professors Paavo Komi, Vesa Linnamo and Ari Heinonen, for giving me a chance on doctoral studies. I hope that by finishing this thesis I have proven myself worthy.

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I owe gratitude to all of the subjects who volunteered in my studies. Quite obviously experimental studies can not be carried out without subjects. I am highly impressed with the altruistic nature of the volunteers, receiving no compensation for their efforts and discomfort.

Last but not least I want to thank my wife Pauliina for her love and support and also my child Evita for unconditional love. Even though I want only the best for you, I also have my own ambitions; e.g. this thesis. Thanks for creating a loving home to return to after a hard day of doing science. I cannot promise that I'll be able to find more time for you now that the thesis work is done, but I can promise I'll always love you.

Jyväskylä 22.6.2010
Timo Rantalainen

FIGURES

TABLES

LIST OF ORIGINAL ARTICLES

I Rantalainen, T., Heinonen, A., Komi, P. V., Linnamo, V. & 2008. Neuromuscular performance and bone structural characteristics in young healthy men and women. European Journal of Applied Physiology 102, 215 - 222.

II Rantalainen, T., Nikander, R., Heinonen, A., Multanen, J., Häkkinen, A., Jämsä, T., Kiviranta, I., Linnamo, V., Komi, P.V. & Sievänen, H., 2010. Neuromuscular performance and body mass as indices of bone loading in pre- and postmenopausal women. Bone 46, 964 - 969.

III Al Nazer, R., Rantalainen, T., Heinonen, A., Sievänen, H. & Mikkola, A., 2008. Flexible multibody simulation approach in the analysis of tibial strain during walking. Journal of Biomechanics 41, 1036 - 1043.

IV Rantalainen, T., Sievanen, H., Linnamo, V., Hoffren, M., Ishikawa, M., Kyrolainen, H., Avela, J., Selanne, H., Komi, P. V. & Heinonen, A., 2009. Bone rigidity to neuromuscular performance ratio in young and elderly men. Bone 45, 956 - 963.

V Rantalainen, T., Linnamo, V., Komi, P.V., Selänne, H. & Heinonen, A., 2010. Seventy-year-old habitual volleyball players have larger tibial cross-sectional area and may be differentiated from their age-matched peers by the osteogenic index in dynamic performance. European Journal of Applied Physiology 109, 651 - 658.

CONTENTS

1 GENERAL INTRODUCTION

Osteoporosis, falls and related bone fractures cause individual suffering and economical burden to the society (Ortiz-Luna et al. 2009, Stevens & Olson 2000). It has been estimated that 30 000 to 40 000 osteoporosis related fractures occur annually and that 400 000 Finnish people have osteoporosis (Suomalainen Lääkäriseura Duodecim 2008). Between the years 1998 and 2000 there were roughly 6000 hip fractures (including only those whom suffered their first hip fracture) annually in Finland. Out of those 6000, more than 90% were suffered by people older than 50 years of age (Kannus et al. 2006, Sund 2006). There are a few potential ways of preventing osteoporosis related fractures, i.e. strengthening bone and/or preventing falls (Ortiz-Luna et al. 2009, Stevens & Olson 2000). Preventing falls is of special interest, as a large proportion of fractures (up to 90%) are caused by falls (Cummings & Melton 2002, Stevens & Olson 2000, Wagner et al. 2009).

Neuromuscular performance (i.e. power production) is related to lower likelihood of falling (Chan et al. 2007, Perry et al. 2007, Sieri & Beretta 2004, Skelton et al. 2002), better functional ability (Foldvari et al. 2000, Runge et al. 2004) and higher skeletal rigidity (Ashe et al. 2008). Aging is associated with weakening of muscles (sarcopenia) (Roubenoff 2000) and bones (osteopenia and osteoporosis) (Carmeli et al. 2002). Since it is currently the consensus that bones adapt to loading (Frost 2000), it seems rational to assume that osteopenias and osteoporoses are a consequence of, or at least partly caused by, sarcopenia (Frost 1997a, Gillette-Guyonnet et al. 2000). Furthermore, the responsiveness of bone to loading seems to decrease with aging (Bassey et al. 1998, Kohrt 2001, Lanyon & Skerry 2001, Suominen 2006). Therefore the purpose of the present thesis was to study the relationship between bone and neuromuscular performance and the effects of aging on this relationship. The studies may be expected to bring new insights into designing osteogenic interventions.

2 REVIEW OF THE LITERATURE

2.1 Bones

The adult skeleton comprises 213 bones (Dempster 2006). One of the fundamental purposes of bones is to provide the body with a rigid and light frame for efficient locomotion (Frost 2000, Frost 2003). In addition, bones help maintain mineral homeostasis and give protection to vital organs (Dempster 2006, Martin & Burr 1989). In order to withstand the prevalent loading without breaking whilst being relatively light, bones have the ability to adapt their structure to functional loading (Frost 2000, Frost 2003). The strength of a whole bone is determined by material and architectural properties (Myburgh et al. 1993, Turner & Robling 2003, van der Meulen et al. 2001). It seems that mechanical adaptation to the imposed loads during a creature's whole life span occurs via adapting the architectural properties of bone rather than altering the material properties (Currey 2003).

2.2 Organization of bone tissue

Bone consists of bone cells (Currey 2002), bone mineral, collagen (Weiner et al. 1999) and bone marrow. In addition, there are blood channels in the bone (Currey 2002).

2.2.1 Bone cells

Bone tissue is permeated and lined with specialized cells (Currey 2002). Osteoblasts derive from osteoprogenitor cells, which differentiate from mesenchymal stem cells in adults. The function of osteoblasts is to produce new bone (Aubin et al. 2006). Osteoblasts lay down new collagen matrix, osteoid, which subsequently mineralizes to form bone (Currey 2002).

Bone-lining cells cover all surfaces of bones including the blood channels (Currey 2002). The outer layer of cells on the bone surface is called periosteum. Periosteum also includes the collagenous sheet covering the outer surface. The layer of cells covering the inner surface of bone is called the endosteum (Morgan et al. 2008). Bone-lining cells are considered to be quiescent osteoblasts and are derived from osteoprogenitor cells (Aubin et al. 2006, Currey 2002).

Osteocytes are the cells in the body of the bone, which are imprisoned in the hard bone tissue (Currey 2002). Osteoblasts become osteocytes when they get trapped within the osteoids they are producing (Burger & Klein-Nulen 1999, Currey 2002). Osteocytes are connected to each other via canaliculi processes, forming, together with the bone-lining cells, a three-dimensional meshwork of interconnected cells covering the whole bone (Burger & Klein-Nulen 1999). The connections between neighboring osteocyte cells are actualized through gap junctions (Currey 2002).

Osteoclasts derive from precursor cells circulating in the blood stream (Currey 2002), which have originated from the bone marrow macrophages (Ross 2006). The function of osteoclasts is to degrade bone. Osteoclast has a ruffled border under which it can dissolve bone (Currey 2002, Ross 2006).

2.2.2 Bone collagen

To a large extent bone is extracellular material, which contributes about 90% of the total bone mass (Robey & Boskey 2006). Bone matrix is composed primarily of type I collagen (85 – 90% of the total protein content), while trace amounts of type III and IV collagen are also present in adult skeleton (Robey & Boskey 2008). Noncollagenous proteins are numerous and while their functions are not well defined, they seem to be multifunctional, participating in mineralization and control of bone turnover (Robey & Boskey 2006). Noncollagenous proteins are secreted to a large extent by bone cells, but about one fourth of noncollagenous proteins are exogenous, mostly serum-derived (Robey & Boskey 2008).

2.2.3 Bone mineral

Of the ~1 kg of calcium in the human body, ~99% is found in bones (Favus & Goltzman 2008). Calcium is incorporated in the bone extracellular matrix as hydroxyapatite. Carbonate, magnesium, acid phosphate and some diet-dependent trace elements are incorporated into the bone hydroxyapatite as substituents (Robey & Boskey 2008). While bone minerals are used in homeostasis, mechanically the main purpose of bone minerals is to provide the compressive strength of the bone composite (Favus & Goltzman 2008, Robey & Boskey 2008).

2.2.4 Mineralized collagen matrix

The basic building block of bone is the mineralized collagen fibril. Collagen acts as a framework for plate –like carbonited apatite crystals (Currey 2002). Together with the carbonited apatite crystals the fibril forms a crystal of nonuniform structure to all three orthogonal directions (Weiner et al. 1999). Mammalian bone can have two forms: woven and lamellar. Woven bone grows rapidly and its collagen is oriented randomly. Lamellar bone grows slowly (Currey 2003) and the collagen fibrils are stacked as layers with rotation between successive layers to produce rotated plywood like structure (FIGURE 1) (Weiner et al. 1999).

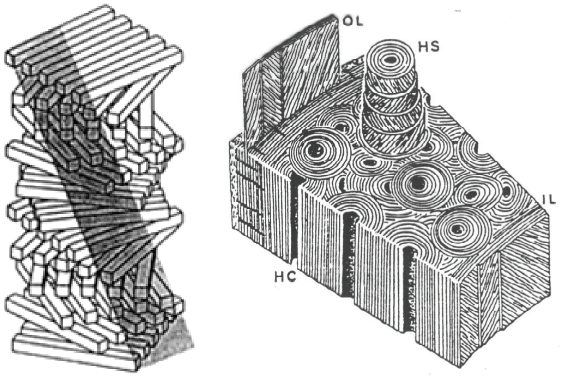


FIGURE 1 Rotated plywood structure seen in lamellar bone material. Illustration on the left from Martin et al. (1998), reprinted with permission from Springer. Illustration on the right from Giraud-Guille (1988), reprinted with permission from Springer.

Secondary remodeling of bone (remodeling is discussed further under heading 2.3) results in production of Haversian bone (Martin & Burr 1989). In Haversian bone much of the bone is occupied by secondary osteons. Primary woven bone (fibrolamellar bone) is superior to Haversian bone in mechanical sense when fibrolamellar bone is loaded along the grain. If however, fibrolamellar bone is loaded transversely against the grain, correctly aligned Haversian bone will be superior in sense of mechanical competence (Currey 2003).

2.2.5 Higher order organization of bone

Bone macro structure can be divided into cancellous (trabecular) and compact (cortical) bone. Compact bone is solid with only spaces being for osteocytes, canaliculi, blood channels and resorption cavities. Cancellous bone in turn is a meshwork of bone material incorporating spaces void of bone material filled with bone marrow (Currey 2002, Dempster 2006). The material making up the bone, cancellous and compact is primary lamellar bone or Haversian bone in adults (Currey 2002). Bones are covered by a fibrous or membraneous sheath. On the outer suface the sheath is called the periosteum and at the inner surface it is called the endosteum (FIGURE 2) (Morgan et al. 2008). Both the peri- and endosteum contain blood vessels, oseoblasts and osteoclasts. In addition, the periosteum contains free nerve endings. Besides the inner surface and trabecular bone, endosteum envelopes the blood vessel canals too (Volkman's canals) (Dempster 2006).

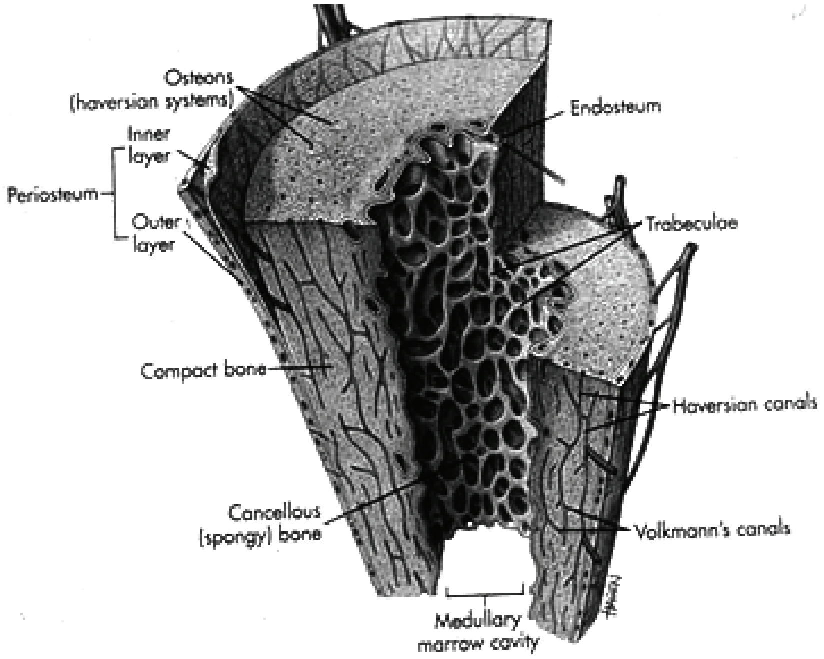


FIGURE 2 Structure of long bone. Modified from University of Bristol & University College Dublin (2001).

There are two main types of bones: flat bones (e.g. skull, scapula) and long bones (e.g. tibia, humerus) (Currey 2002). Long bones consist of a hollow tube, the diaphysis, the cone-shaped ends below the growth plates, metaphyses and the regions above the growth plate, the epiphyses (Dempster 2006). Long bones are hollow and the cavity is filled by marrow fat in adults (Guyton & Hall 2000). The marrow fat serves no essential purposes, although it may play a role in increasing the ability of bone to withstand compressive loading by preventing buckling (Currey 2003). Part of the marrow remains red also in adults and produces red blood cells (Guyton & Hall 2000). This kind of arrangement decreases the weight of long bones by approximately 15% compared to correspondingly stiff solid bone from the same material (Currey 2003).

2.3 Bone modeling and remodeling

Bone modeling is the process, which determines the overall shape of the bone during growth. In modeling the bone growth is retarded at some places whereas in other places the bone growth is facilitated. Bone mineral accumulation caused by modeling can be facilitated via increased mechanical usage and decreased by decreased mechanical usage (Frost 1985). Bone modeling occurs on the bone outer surfaces, whereas remodeling occurs within the bone in the mineralized matrix (Martin & Burr 1989).

In remodeling, bone material is turned over by resorption by osteoclasts and formation by osteoblasts (Frost 1985, Martin & Burr 1989). Remodeling leads to increased skeletal mass if more bone is produced by the osteoblast than what is resorbed by the osteoclasts. In adults remodeling predominates as the mechanism responsible for skeletal adaptation (Frost 1985). Remodelling is also used to repair microcracks caused by loading and fatigue of the bone material (Currey 2003).

2.3.1 Mechanotransduction

The translation of physical activity to cellular responses is called mechanotransduction (Turner & Pavalko 1998). The bone response occurs ultimately at the cellular level (Rubin & Rubin 2006). The current view of the mechanism responsible for mechanosensing is that fluid flow in bone tissue caused by deformation of bone is sensed by the osteocytes (Rubin & Rubin 2006, Turner & Pavalko 1998). Local architecture determines the loading a particular bone location observes. For example, in bending cortical bone endures higher pressure gradient than trabeculae. Furthermore, different bone locations may have differing loading thresholds or be sensitive to loading in certain directions (Lanyon & Skerry 2001).

Bone remodeling cycle is initiated by mechanical signals via cellular mechanotransduction. Mechanotransduction consists of four distinct phases: 1) mechanocoupling, force applied to the bone is transduced into a local mechanical signal perceived by a sensor cell; 2) biochemical coupling, the transduction of a local mechanical signal into a biochemical signal; 3) transmission of signal from the sensor cell to the effector cell and 4) the effector cell response, the appropriate tissue-level response (Turner & Pavalko 1998).

During daily activities multiple mechanical factors arise in the bone tissue (Rubin & Rubin 2006). Daily activities cause deformation, pressure, transient pressure waves, shear forces and dynamic electric fields. Of these possible stressors deformation and shear (strains) have been isolated as the most significant mechanical events for bone. All of the bone cells seem to be able to respond to mechanical signals (Rubin et al. 2006). However, osteocytes seem to be advantageously situated (Martin & Burr 1989) and the microarchitecture is favourable for mechanosensing as the architecture causes amplification of the signal (Han et al. 2004, Rubin et al. 2006). The exact type of mechanosensors is yet to be revealed in bone cells, but the sensing of mechanical event leads to alteration in appropriate ion channel activities which ultimately leads to change in the activity of the cell (Rubin et al. 2006, Turner & Pavalko 1998). Mechanical signals ultimately activate mitogen-activated protein kinase (MAPK) regardless of the cell (Rubin et al. 2006) and the response depends on the gene patterns associated with the target cell (Rubin et al. 2006, Turner & Pavalko 1998).

2.3.2 Bone remodeling cycle

Remodelling cycle begins with recruitment of osteoclasts to the bone surface. Osteoclasts cause breakdown of the collagen matrix of bone and release of calcium and other minerals (Watts 1999). Osteoclastic resorption begins when osteoclast attaches to mineralized bone matrix and produces tight ring-like sealing zone. The plasma membrane opposite to bone and inside the sealing zone becomes ruffled and the resorption lacuna develops between the bone and the ruffled border membrane. Osteoclast releases acid to the resorption cavity, which will lead to degradation of the bone. Osteoclast endocytoses the degradation products (calcium, phosphate and collagen framents) through the ruffled border. The degradation products are thereafter released to the extracellular space (Väänänen 2005). When osteoclasts have done their degrading they presumably die (Currey 2002).

After osteoclastic resorption the osteoblasts fill the resorption cavity with protein matrix called osteoid, which is mineralized subsequently (Watts 1999).

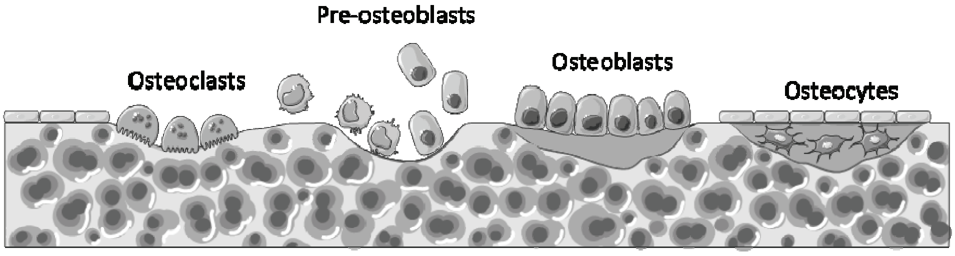


FIGURE 3 Bone remodeling cycle advancing from left to right. Adapted from Les Laboratories Servier (2005).

The cells involded in the remodeling are refferred to as a basic multicellular unit (BMU). Typically resorption phase lasts 7 – 10 days and formation 2 – 3 months (FIGURE 3) (Watts 1999). Mineraliztion of the newly formed matrix begins after a lag time of ~two weeks and proceeds rapidly within a few days up to about 70% of the mineralization capacity. Then subsequent residual mineralization up to the full capacity takes several years (Fratzl et al. 2004). About 10% of bone material is replaced annually (Watts 1999).

2.3.3 Non-mechanical factors affecting bone metabolism

Remodeling is regulated by local and systemic factors, which include: electrical and mechanical forces and multiple chemical factors such as hormones (TABLE 1) (Christenson 1997, Watts 1999). In addition to calciotropic hormones (parathyroid hormone, vitamin D and calcitonin), which play a major role due to their role in metabolism, gonadal steroid (sex) hormones, play an important modulatory role in modeling and remodeling. Gonadal hormones regulate the maturation of the skeleton and the maintenance of bone mass (Venken et al. 2008).

TABLE 1 Chemical factors affecting bone metabolism. Reproduced from Christenson (1997).

Factor	Effect on turnover	Cells effected	Mechanism
Parathyroid hormone	Increase	Osteobasts	Increased osteoclast activation and accelerated bone loss
Thyroxine	Increase	Osteoclasts	Increased resorption
Estrogen	Decrease[sic]	Osteoblasts	Deficiency causes accelerated bone loss
Testosterone	Decrease	Osteoblasts	Deficiency causes accelerated bone loss
Vitamin D	Decrease	Osteoblasts	Deficiency causes increased activation but inhibits mineralization of osteoid matrix
Cortisol	Increase	Both	Increased resorption and inhibition of formation leading to accelerated bone loss
Calcitonin	Decrease	?	Inhibits resorption
Insulin	Decrease	Osteoblasts	Increased collagen synthesis

Steroid hormones modulate the bone turnover by influencing osteoclast and osteoblast metabolism both by modulating gene expression and nongenomically by influencing the cell metabolism (Secreto et al. 2006). The important modulatory role of gondal steroids is highlighted by the menopause related marked bone loss in women (Venken et al. 2008).

From nutritional view point, the needs of bones can be met with balanced diet. Of the micronutrients, calcium and vitamin D play crucial roles in bone metabolism. Calcium needs can be met by consuming nutrients rich in calcium, such as milk and cheese (Nieves 2005). For vitamin D, especially in areas with limited sunlight exposure (i.e. latitudes above 40 ° latitude) supplementation in the form of fortified foods and/or as supplements may be beneficial for bone health (Feldman et al. 2008, Nieves 2005).

2.3.4 Bone turnover

Bone turnover rate may be estimated from biochemical markers (Watts 1999) analyzed from blood or urine samples (Weisman & Matkovic 2005) by comparing the ratio of resorption markers to formation markers (Christenson 1997). Bone turnover rate, measured by the rate of bone multicellular unit activation frequency is high in childhood, decreases to a minimum towards the age of 35 years of age rises to a second peak at approximately 60 years of age and thereafter declines again towards the end of the life span (Martin & Burr 1989).

2.4 Assessing skeletal rigidity

Whole bone strength can be measured directly by mechanically loading the bone and measuring the load at which the bone fails. Structural stiffness and strength may be obtained by this kind of direct testing. Structural stiffness and strength depend on the material properties as well as the geometry of the structure. Therefore neither material properties nor geometry alone adequately describes the strength of a whole bone (Myburgh et al. 1993, Turner & Robling 2003, van der Meulen et al. 2001).

The relationship between the applied load and deformation caused by the load can be plotted as a load-deformation curve. The curve may be divided into two parts, the linear elastic region and the non-linear plastic region. The stiffness of the structure is the slope of the elastic region, yield is the load at transition from the linear to elastic region and toughness is the area under curve up to yield or failure (FIGURE 4) (Currey 2001, Martin & Burr 1989, Turner & Burr 1993).

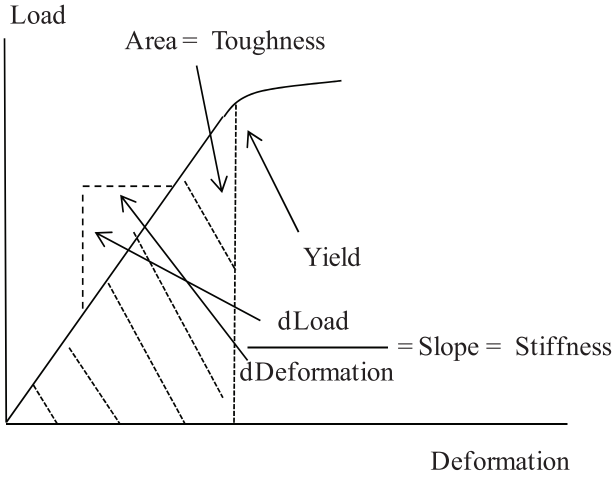
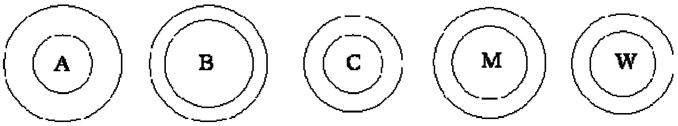


FIGURE 4 Schematic illustration of a load-deformation curve.

The load-deformation curve may be converted to stress-strain curve by accounting for the geometry of the structure and loading situation. The slope of the stress-strain curve in turn is the Young’s modulus, i.e. stiffness, of the material. The strength of the structure is defined as the load at which the structure either yields (yield strength) or breaks (breaking strength, which ~equals ultimate strength in bone). As was the case with stiffness, the strength may be reported as a material property (yield or breaking stress) or structural property (yield or breaking load). Because of the plywood structure of bone material, Young’s modulus and breaking stress are different in longitudinal and transverse directions. Furthermore, bone ultimate stress is different in tension, compression and shear. While looking at different types of loadin bending, compression and shear, it becomes obvious that the geometry of bone is of utmost importance in bending and shear loading (Currey 2001, Turner & Burr 1993).



Radius (in / out)	1 / 0.5	1 / 0.75	0.83 / 0.5	0.95 / 0.63	0.86 / 0.56
Relative area/ Compressive strength	1	0.58	0.58	1	0.87
Relative stiffness	1	0.73	0.44	1	0.71
Relative strength	1	0.73	0.53	1	0.78

FIGURE 5 Influence of bone geometry on compressive strength, bending stiffness and bending strength. Modified from Currey (2001). A: a circular cross-section of a tube (~bone). B: The wall thickness is reduced to half of the value in A, while the outer radius is identical to A. C: The wall thickness is reduced from the outer surface in such a way that C and B have identical cross-sectional areas. M: The average values of total and cortical cross-sectional area of tibia from 20-29 year old men normalized to starture from Riggs et al. (2004) converted to a circular cross-section. W: the values corresponding to M for women. To produce relative values, the values for cross-sections A – C are divided by the values of A and the values for cross-sections M and W are divided by the values of M.

It is thought that bones are primarily loaded in bending and compression (Biewener 1991, Garcia & da Silva 2004, Morgan et al. 2008) and therefore these two types of loadings are used as an example. In compression (or tension), the stiffness of the structure depends purely on the amount of material in a given cross-section and on the Young's modulus of the material (Currey 2001). In bending, however, similar structural stiffness may be achieved with infinite number of combinations of amounts material and geometry, when Young's modulus is kept constant. In effect, with the same amount of material, the bone is stiffer, the further away from the center of mass the material is situated, and furthermore the effect on structural stiffness increases to the square of the distance from the center of mass. The stiffness of a given structure is directly related to the cross-sectional moment of inertia (a.k.a. second moment of area, area moment of inertia) (Bouxsein 2005). However, if the cortex becomes too thin the structure becomes susceptible to buckling, and thus there is a limit how far from the center of mass the material can be situated (Currey 2001). Cross-sectional moment of inertia of a circular cross-section is calculated as:

Equation 1 $CSMI = \frac{\pi}{4}\left(r_2^2 - r_1^2\right)$,

where r2 = outer radius of the cross-section and r1 = inner radius of the cross-section. The bending strength of a circular tube is dependent on the cross-sectional moment of inertia divided by the outer radius of the cross-section (FIGURE 5).

Obviously, mechanical testing to failure is not feasible *in vivo*, and therefore indirect ways to estimate skeletal rigidity (e.g. densitometry) are regularly employed (Turner & Burr 1993). Assessment of bone strength should take shape and size of the bone into account (Myburgh et al. 1993, Turner & Robling 2003). Long bone stiffness can be estimated non-invasively by mechanical response tissue analysis (MRTA), which predicts relatively accurately the stiffness measured by three point bending (Roberts et al. 1996). In the indirect imaging based estimation methods planar dual energy x-ray absorptiometry (DXA) (Beck et al. 1990, Järvinen et al. 1998, Sievänen 2000)) or cross-sectional scan/scans such as magnetic resonance imaging (MRI) and quantitative computed tomography (QCT) are applied. Skeletal rigidity is estimated based on material and architectural properties assessed from the images. Imaging based predictions of skeletal rigidity, accounting for both geometry and material stiffness, offer reasonable estimates of actual rigidity (Beck et al. 1990, Hudelmaier et al. 2004, Järvinen et al. 1998). Ultrasound measurements are also used to estimate mineral quantity or material stiffness, but as indicated above, the bone strength estimates based solely on material quantity are not as good as the ones also including geometry (Hudelmaier et al. 2004).

3 NEUROMUSCULAR SYSTEM

3.1 Organization of skeletal muscle

The primary function of muscles is to produce force and movement (Lieber & Bodine-Fowler 1993). Contraction velocity and the range of motion of a given muscle are dependent on the number sarcomeres in series and the strength of force of the contraction is dependent on the number of parallel sarcomeres (Lieber & Bodine-Fowler 1993). The way the fibers are arranged is called muscle architecture and typical examples found in humans include pennated muscles, in which the fibers are arranged at an angle to the longitudinal axis of the muscle (Fukunaga et al. 1997). Muscle architecture affects the force output of the muscle as well as the range of motion and the shortening velocity. If two muscles with equal length and volume are considered, the one with smaller pennation angle has longer muscle fibers, less parallel fibers, greater shortening velocity and larger range of motion whereas the one with the larger pennation angle produces more force (Lieber & Bodine-Fowler 1993).

3.2 Muscular force production

Force is developed in the muscle via cross-bridge cycling, known as the sliding filament theory (Huxley 2000, Rassier et al. 1999). The sliding filaments are actin and myosin molecules. Myosin heavy chain froms the cross-bridges between actin and myosin, and the force is produced by conformational changes of myosin heavychains during hydroxylation (Huxley 2000). Force is transmitted longitudinally from Z-band to Z-band, whilst the most distal Z-band is attached to the myotendinous junction (Bloch & Gonzalez-Serratos 2003). However, not all of the muscle fibers reach the myotendinous junction and moreover, many muscle fibers taper towards the ends. If there were no lateral force transmission system, the forces produced by the larger cross-section at the fiber mid-section would be wasted as the smaller crossection near the end of the fiber could not sustain the force. Fortunately, the forces are transmitted via structural proteins (e.g. vinculin, dystrophin) laterally to sarcolemma (Monti et al. 1999). From the sarcolemma, the force is futher transmitted laterally to the extracellular matrix and to the connective tissues. The sites of lateral force transmission are called costamers comprising membrane-cytoskeletal complexes (Bloch & Gonzalez-Serratos 2003).

3.3 Neural control of muscular force production

The smallest unit of force production that can be voluntarily activated is a motor unit. Motor unit is the final common pathway from central neural system to the muscle and comprises a motor neuron and the muscle fibers innervated by the motor neuron. There are three basic types of motor units; slow fatigue resistant, fast fatigue resistant and fast fatigable (English & Wolf 1982). Motor units are recruited in an orderly fashion from the smallest to the largest, a phenomenon known as the Henneman size principle (Henneman et al. 1965). According to Henneman (1965) the neural circuits at the spinal level are apparently organized in such a way that each motor unit receives approximately equal excitatory drive regardles of the source (e.g. afferent or efferent pathways) and the recruitment order is determined by the smaller units getting larger excitatory post synaptic potentials due to their higher input resistance (Henneman et al. 1965). Force output is controlled by recruiting new motor units and modulating the firing rate of active motor units. In addition, the amout of firing doublets and synchronization (common drive) of motor units affect the force production (Kamen 2005).

3.4 Converting force production to movement

The force produced by muscles is transmitted to the skeleton via tendons. The forces cause movement of bones relative to each other (Moore & Dalley 1999). In effect, the forces produced by muscles are manifested as torques, and torques depend not only on the force but also on the moment arm (Rassier et al. 1999). A similar torque may be produced with infinite combination of torques and moment arms and therefore it is impossible to tell whether a strong person has large moment arm or if the person’s muscles produce abnormally high force unless the moment arm is measured (Lieber & Bodine-Fowler 1993). However, in some joints the centre of rotation changes as a function of joint angle because of the anatomy of the joint and furthermore the moment arm and direction of pull of muscles depends on the joint angle, making defining moment arm a challenging task (Maganaris 2004). The active joint range of motion (i.e. the range over which the muscle is able to produce force) is defined by the distance from the insertion of the muscle and the joint axis (Rassier et al. 1999). The further away the muscle is inserted the lower is the joint range of motion. Remembering that pennate muscles (with similar muscle length and volume) have shorter fibers and therefore shorter range of motion, inserted at a similar distance from the joint centre will have shorter joint range of motion. However, in humans there is a positive correlation between fibre length and the distance from the insertion to the joint axis and therefore there is no rule of thumb on the physiological role of a given muscle based on its architecture (Lieber & Bodine-Fowler 1993).

3.5 Neural control of locomotion

Controlling even simple locomotor tasks (e.g. walking) requires repetitive coordinated excitation pulse trains to several muscles. If all of these excitation pulse trains were voluntarily controlled, little attention could be paid to the surroundings because of the constant task of coordinating muscles. Since locomotion has been essential for survival, efficient ways to control locomotion have evolved. Only rhythmic excitation bursts are required for a locomotory pattern to emerge. The volitional load is further reduced by, central pattern generator (CPG) neural circuits, which produce the rhythmic excitation bursts required. CPGs need only be activated volitionally, after which they are able to produce rhythmic excitations independently of peripheral feedback (Capaday 2002, Hultborn 2006, Ijspeert 2008). Furthermore, the rhytmic locomotory pattern may be modulated by peripheral feedback automatically (i.e. reflexes) or voluntarily (Ijspeert 2008).

Several different afferent pathways exist in humans (i.e. proprioception); however, the stretch reflexes are probably the most important for locomotion (Yakovenko et al. 2004, Zehr & Stein 1999). The stretch reflex originates from the muscle spindle. Muscle spindles are stretch velocity and magnitude sensitive with increasing activity with increasing stretch intensity (Matthews 1933). The simplest and quickest modulation of movement occurs with the monosynaptic stretch reflex, which travels to the spinal cord via Ia-afferent from the muscle spindle and excites an α-motoneuron innervating the homonymous muscle (Matthews 1959). The activity of the muscle spindle also facilitates other agonists while it inhibits the antagonist and contralateral agonist (Hultborn 2006). Furthermore, the activity burst originating from the muscle spindle is transmitted via polysynaptic pathways up to and including the cerebral cortex, which is manifested as long latency activity burst following a stretch (Christensen et al. 2000). Reflexes play an important role in coordinated movements and particularly in stretch shortening cycle type dynamic movements, such as running and jumping (Komi & Gollhofer 1997). Therefore aging/disease (e.g. diabetes/polyneuropathy (Bloem et al. 2000), crebrellar ataxia (Morton & Bastian 2004)) related decline in reflex responses may be manifested in deterioration of locomotion and/or postural balance (Bloem et al. 2000, Morton & Bastian 2004).

4 EFFECTS OF AGEING ON THE NEUROMUSCULOSKELETAL SYSTEM

Aging is associated with degeneration of the nervous system (Lexell 1997, Verdu et al. 2000), loss of muscle mass, weakening of muscles (sarcopenia) (Roubenoff 2000) and performance (dynapenia) (Clark & Manini 2008). The degeneration of the nervous system is manifested as reduction in the numbers of motor units (Lexell 1997, Verdu et al. 2000) and reduction in the sensitivity of the proprioceptive system (Shaffer & Harrison 2007). The stretch reflex sensitivity decreases, which leads into longer reflex latencies and smaller amplitudes associated with longer durations of muscle activations (Shaffer & Harrison 2007, Tang & Woollacott 1998, Tang & Woollacott 1999). The changes in proprioception ultimately lead to decline in postural balance with aging (Shaffer & Harrison 2007). Beyond 60 years of age muscle mass declines by ~1% per year, strength 1.4 to 2.5% per year and power production capacity by ~3.5% per year (Faulkner et al. 2007, Vandervoort 2002). At least part of the atrophy is caused by deinnervation (Lexell 1997, Verdu et al. 2000). The faster decline in performance compared to the muscle mass may be attributed to 1) loss of motor units and selective denervation of fast motor units (Faulkner et al. 2007, Vandervoort 2002), 2) slowing of muscle fiber shortening velocity (Barry & Carson 2004, Deschenes 2004), 3) decrease in myofiber specific tension (Deschenes 2004), 4) changes in muscle architecture (Narici et al. 2003) and 5) decreasing neural activation (Clark & Manini 2008).

4.1 Gender differences in skeletal robusticity

Men have substantially more rigid skeleton than women when normalized to body height (Riggs et al. 2004) or muscle mass (Melton et al. 2006). However, women exhibit an estrogen related mineral packing during puberty, presumably to meet the needs of pregnancy and lactation, which causes women to have higher bone mineral to lean body mass ratio during the fertile years (Ferretti et al. 1998, Ferretti et al. 2003, Järvinen et al. 2003, Schiessl et al. 1998). The "extra" mineral is deposited to endosteal surface and trabecular bone sites (Järvinen et al. 2003). Consequently, postmenopausal bone loss is more marked in trabecular bone (Reid 2008, Sievänen et al. 1999). From mechanical point of view, for equally stiff bones between fertile woman and a man of similar size, the extra mineral deposited to endosteal surface, would render the endosteal and periosteal diameter smaller in fertile woman compared to the man, whereas the cortical wall would be thicker (Schoenau et al. 2002). This also appears to be the case, as men have more robust skeletons than women (Melton et al. 2006, Riggs et al. 2004).

4.2 Bones and aging (osteopenia and osteoporosis)

Bones weaken with age (Riggs et al. 2004) a phenomenom called osteopenia (Carmeli et al. 2002). According to the World Health Organization definition, osteopenia is defined as a bone mineral density (BMD) or content (BMC) between one to two and a half standard deviations (SD) below the young female average. Osteoporosis in turn is defined as a BMD or BMC more than 2.5 SDs below the young female adult average (World Health Organization 1994). Osteoporosis is especially prevalent in females, probably because of the female reproductive hormone, estrogen, which appears to play a major role in postmenopausal bone loss (Type I osteoporosis) (Järvinen et al. 2003, Riggs et al. 2004). Postmenopausal bone loss is more marked in trabecular bone, which is reflected in early menopausal fractures occurring in areas ritch in trabecular bone. The perimenopausal bone loss is driven by accelerated bone turnover with a negative balance (Reid 2008). There is also an increasing prevalence of male osteoporosis with advanced age (type II, or senile osteoporosis)(Kaufman & Goemaere 2008). Apart from the postmenopausal bone loss, the mechanisms of age related bone loss between men and women appear to be similar. Bone resorption is increased whereas no change or decerease orrcurs in bone formation (Kiel et al. 2008).

4.3 Role of neuromuscular changes in skeletal deterioration

There are several suggestions as to why age related bone loss (type II, or senile osteoporosis) occurs. Mechanical reasons have been suggested in the form of disuse bone loss. Since it is currently the consensus that bones adapt to loading (Frost 2000), it seems rational to assume that osteopenias and osteoporoses are a consequence of, or at least partly caused by, sarcopenia (Frost 1997a, Gillette-Guyonnet et al. 2000). Moreover, during the childhood and adolescence the increase in skeletal rigidity appears to follow the increase in skeletal muscle mass rather tightly (Daly et al. 2004, Schoenau & Frost 2002, Schoenau et al. 2002).

During aging however, skeletal rigidity appears to decrease less than what would be expected from the decline in skeletal muscle mass (Melton et al. 2006), which indicates that the responsiveness of bone to loading may decrease with aging (Bassey et al. 1998, Kohrt 2001, Lanyon & Skerry 2001, Rubin et al. 1992, Suominen 2006). Furthermore, nonmechanical factors also paly a role in age related bone loss i.e. nutritional (vitamin D, calcium, caloric malnutrition), hormonal (estrogen, androgens) and heritable factors (Kiel et al. 2008).

5 SKELETAL LOADING

The forces applied to bone are primarily caused by muscles. Muscle forces, due to the shorther moment arms of the muscles compared to the moment arms of the distal joints the muscles are moving, are greater than the forces caused by gravitational pull on body weight (Burr et al. 1996).

5.1 Loading imposed by neuromuscular system

Bones are loaded in daily activities by muscles, fighting the pull of gravity and accelerating and decelerating body segments. It has been demonstrated that physical activity in the general population affects more strongly the weight bearing skeleton (Mikkola et al. 2008), and therefore, it may be argued that skeletal system is loaded mainly in locomotory actions. The loading on bones caused by neuromuscular system apparently decreases with aging as a consequence of sarcopenia and decrease in physical activity (Westerterp 2000). Even if physical acitivity is maintained as in the case of master athletes, the effects of sarcopenia evidently decrease skeletal loading with aging (Faulkner et al. 2007).

One way of estimating the loading caused by locomotory actions is from the ground reaction forces registered during those actions. The ground reaction forces during locomotion vary from 1.0 to 2.9 times body weight in walking and running at low speeds (up to 6.0 m/s) (Nilsson & Thorstensson 1989), 2 to 2.5 times body weight in counter movement jump (Fukashiro & Komi 1987, Nikander et al. 2006), to 3 to 4.5 times body weight in running at maximal speed (Belli et al. 2002, Nummela et al. 1994) and 4 to 8 times body weight in continuous rebound jumping and drop jumping (Fukashiro & Komi 1987, Ishikawa et al. 2005b). In athletic events ground reaction forces in excess of 10 times body weight have been recorded (Perttunen et al. 2000). The magnitude of tibial midshaft *In vivo* strains have been measured during several dynamic activities, e.g. 300 με in bicycling (Milgrom et al. 2000b), 300 - 800 με in walking (Burr et al. 1996, Ekenman et al. 1998, Lanyon et al. 1975, Milgrom et al. 2000b, Milgrom et al. 2001), 600 – 1400 με in running (Burr et al. 1996, Ekenman et al. 1998, Lanyon et al. 1975, Milgrom et al. 2000a, Milgrom et al. 2000b, Milgrom et al. 2001) and 700 - 2000 με in jumping (Ekenman et al. 1998, Milgrom et al. 2000a, Milgrom et al. 2001).

Combining the ground reaction force measurements with tibial mid-shaft strain measurements appears to reveal a non-linear relationship, as ground reaction forces increased four- to five fold from walking to continuous jumping, whereas bone strains increase more in the order of two to threefold. Considering the joint moments in typical locomotory actions for ankle and knee, the body weight normalized values vary from 1.5 Nm/kg and 0.8 Nm/kg in walking (Silder et al. 2008) to 3.1 Nm/kg and 2.2 – 3.7 Nm/kg in running (Belli et al. 2002) to 1.4 – 4.8 Nm/kg and 1.9 – 6.0 Nm/kg (Fukashiro & Komi 1987, Stefanyshyn & Nigg 1998) for ankle and knee joint respectively. In case of ankle joint moments there appears to be a two- to threefold increase from walking to running and jumping, which is in line with the respective increase in bone strains. For the knee joint moment the increase is three- to fivefold, which is in line with the increase seen in the ground reaction forces.

5.1.1 Ground reaction forces and tibial diaphysis strains

The relationship between ground reaction forces and skeletal loading is not really straightforward. The moment arm of the ground reaction forces depends on the posture of the body as well as the moment arms of the muscles. Ground reaction forces and Achilles tendon force measured in walking are next used as an illustrative example (FIGURE 6). Typically two peaks are seen in the vertical ground reaction force during walking, the first of which occurs during heel strike and weight acceptance and the second during the push-off phase. However, in Achilles tendon force only one peak is seen, which coinsides with the push-off phase (Komi et al. 1992). Furthermore, apparently the bone is loaded in a completely different manner during these two peaks observed in the ground reaction force. During the heel strike, while there is little or no force produced by the ankle extensors, the bone is apparently loaded only by the ground reaction force, whereas during the push-off phase the Achilles tendon force is summated with the ground reaction force to double or triple the loading compared to heel strike a pattern seen in maximum and minimum strain in *in vivo* measurements (FIGURE 6) (Lanyon et al. 1975). Similar discordance between ground reaction force and tendon forces has been observed in jumping for Achilles tendon and for Patella tendon (Finni et al. 2000). While looking at joint moments calculated with inverse dynamics from kinematic and kinetic measurements (Silder et al. 2008), the ankle joint moment pattern corresponds rather closely with the in vivo tibial mid-shaft strain. Interestingly, the 1st and 2nd peaks in the strain curve, absent in the ankle joint moment seem to correspond to the peaks in hip and knee moments (FIGURE 6). Taken together, the aforementioned highlight the difficulties in inferring skeletal loading from ground reaction force measurements.

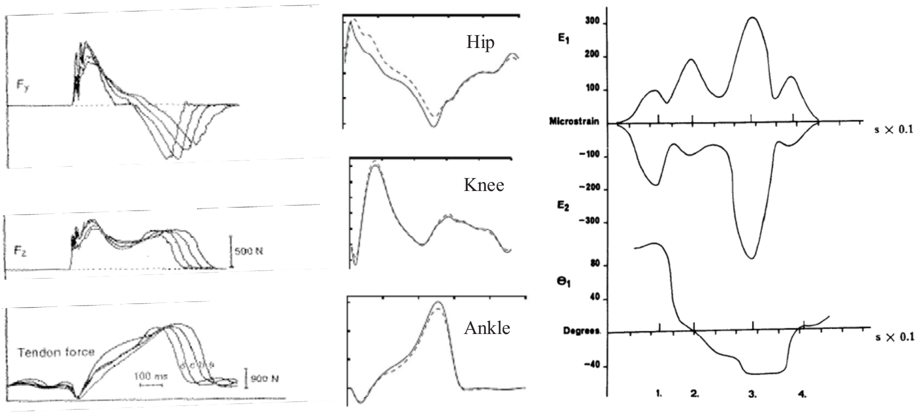


FIGURE 6 Left pane: horizontal (antero-posterior) and vertical ground reaction forces and Achilles tendon force during strides with different walking velocities. Modified from Clinics in sports medicine, 11, Komi, P.V., Fukashiro, S. & Järvinen, M., Biomechanical loading of Achilles tendon during normal locomotion, 521-531., Copyright (1992), with permission from Elsevier. Middle pane: joint moments in walking. Adapted from Journal of Biomechanics, 41, Silder, A., Heiderscheit, B. & Thelen, D.G. 2008. Active and passive contributions to joint kinetics during walking in older adults. 1520-1527., Copyright (2008), with permission from Elsevier. Right pane: maximum and minimal principal strain during one ground contact in walking. Reproduced from Lanyon et al. (1975) with permission from Taylor & Francis.

5.1.2 Loading caused by the vibration of the muscles

Recently it has been observed that bones respond to low amplitude vibration delivered at a 15 – 90 Hz frequency, which corresponds with the frequencies observed in muscles during voluntary force production (Rubin et al. 2006). The firing rates of individual motor units vary from ~5 to ~60 Hz (Connelly et al. 1999, Roos et al. 1999), and these frequencies are also present in the mechnical vibration of the muscle during activation (Orizio et al. 1996). Evidently the tremor observed in total force output is not related to the rate of individual motor unit firing rates as physiological tremor occurs at ~10 Hz frequency. Tremor apparently originates from the common drive to motor units, from central neural circuits (brain) and from peripheral circuits (spinal reflex loops) (Zhang & Poignet 2009).

5.2 Bone and exercise

Mechanical loading of bone affects the quality and quantity of human bones when adequate nutrition and hormonal balance is available (Smith & Gilligan 1996) causing an appropriate adaptation in bone structure and mass (Frost 2003, Lanyon & Skerry 2001). If new forces outside normal loading range are introduced, bones will adapt to accommodate the new loads. If loading remains constant no additional bone formation occurs after bones have adapted to the new loading level (Cullen et al. 2000, Frost 2003, Lanyon & Skerry 2001). This adaptation to mechanical loading has been demonstrated in numerous studies of athletic populations (Haapasalo et al. 2000, Heinonen et al. 2001, Heinonen et al. 2002, Kontulainen et al. 2003, Nikander et al. 2005, Nikander et al. 2006, Nikander et al. 2009) and interventions in different age groups from adolescent (Hind & Burrows 2007) to elderly (Schmitt et al. 2009). Adolescence, especially prior to cessation of linear growth, appears to be the most opportune timing for manipulating the skeletal rigidity (Guadalupe-Grau et al. 2009, Hind & Burrows 2007) but skeletal rigidity may be maintained or even increased with exercise in the adults and elderly (Schmitt et al. 2009). Effective exercises include explosive actions and/or loading from unusual directions (Guadalupe-Grau et al. 2009, Heinonen 1997, Hind & Burrows 2007, Nikander et al. 2005, Nikander et al. 2006, Nikander et al. 2009, Schmitt et al. 2009).

5.2.1 Osteogenicity of exercise

The osteogenic effect of exercise increases when the interval between loadings is increased inside an exercise bout thus allowing the bone to recover from the load (Umemura et al. 2002). In a classic study, Rubin & Lanyon (1984) discovered with rooster ulnas that bone mass can be maintained with only a few osteogenic strain cycles (4 cycles per day taking 8 seconds in total) comparatively infrequently. Increasing the number of strain cycles / day resulted in increased bone formation. However, increasing the number of strain cycles above 36 cycles / day did not result in any additional bone mineral accrual. The strain applied was comparable to normal physiological wing flapping strains (Rubin & Lanyon 1984). Bone formation increases with increasing loading cycles when the intensity is held constant and the strain magnitude is not high. If intensity of the loading is increased the number of loading cycles required for response decreases (Cullen et al. 2001).

5.2.2 Osteogenic index

An osteogenic index (OI), which is the product of strain magnitude and rate, may help estimate the effects of performance technique to the osteogenicity of a given exercise (Turner 1998, Turner & Robling 2003, Whalen et al. 1988). While osteogenic index is mainly based on animal models, it has been proposed that the results may be extrapolated to designing osteogenic exercise regimes for humans as follows (Turner & Robling 2003):

Equation 2 $$OI = \sum_{i=1}^{i} GRF_i * \ln(N_i + 1) * \left(1 - e^{-t_i/6}\right),$$

Where i = the index of a given exercise bout, GRF = the average ground reaction force of the exercise in terms of multiples of body weight, N = number of loading cycles, t = time in hours from the previous bout of exercise

Even though osteogenicity depends on strain magnitude and rate, only magnitude is included in Equation 2 and the OI is calculated from ground reaction force instead of bone strains. With certain limitations, for the purposes of OI calculations, it may be assumed that bone strains depend on the ground reaction forces. Furthermore, again for the purposes of calculating an OI, it may be assumed that loading rate depends on the loading magnitude.

Von Stengel et al. (2005, 2007) have reported some results concerning the applicability of osteogenic index in humans. In their study on postmenopausal women, better osteogenic results were obtained using higher loading rates, i.e., using power training approach instead of strength training approach. In other words, power training produced larger gain in skeletal rigidity. Magnitude or number of repetitions did not differentiate the exercise regimes from each other, whereas osteogenic index was shown to be able to differentiate the power training from strength training (von Stengel et al. 2005, von Stengel et al. 2007).

5.3 Assessing skeletal loading

Skeletal loading may be assessed in several ways: by questionnaires asking how much and what types of exercise people do, by measuring body mass or neuromuscular performance, by recording accelerations of the body over a period of time or by actually measuring the deformation of bone *in vivo*. Obviously directly measuring the deformations would give one the most accurate assessment of the bone loading environment. However, in vivo measurements are invasive and limited to only superficial bones (Hoshaw et al. 1997). Questionnaires on the other hand offer a relatively easy way of estimating skeletal loading. However, questionnaires have been shown to be relatively unreliable (Westerterp 2009).

Measuring body mass or neuromuscular performance offers another quick and relatively easy way to estimate skeletal loading environment. Moderate associations have been observed between neuromuscular performance and indices of skeletal rigidity (Ashe et al. 2008, Blain et al. 2001, Nikander et al. 2006, Sandstrom et al. 2000, Sievänen et al. 1996a, Taaffe et al. 1995, Taaffe & Marcus 2004). Recording accelerations of the body over an extended period of time appears to be a reasonable way of assessing skeletal loading environment (Heikkinen et al. 2007, Vainionpää et al. 2005, Vainionpää et al. 2006, Vainionpää 2007), especially considering that skeletal adaptation is relatively slow.

5.4 Muscle bone interaction

The association between muscle and bone has been studied by measuring fat free mass (Blain et al. 2001, Capozza et al. 2004, Henderson et al. 1995, Pettersson et al. 1999, Rector et al. 2009, Taaffe et al. 2001, Witzke & Snow 1999), performance (Ashe et al. 2008, Blain et al. 2001, Calmels et al. 1995, Halle et al. 1990, Madsen et al. 1993, Pettersson et al. 1999, Sandstrom et al. 2000, Sinaki & Offord 1988, Snow-Harter et al. 1990, Taaffe et al. 1995, Taaffe et al. 2001, Taaffe & Marcus 2004, Witzke & Snow 1999, Zimmermann et al. 1990) and bone or by developing regression models, in which neuromuscular performance is included as an independent variable in addition to body size (Ashe et al. 2008, Blain et al. 2001, Capozza et al. 2004, Henderson et al. 1995, Madsen et al. 1993, Nikander et al. 2006, Snow-Harter et al. 1990, Taaffe et al. 1995, Taaffe et al. 2001, Witzke & Snow 1999). The Pearson correlation coefficients between lean mass and skeletal rigidity have been found to range between 0.34 and 0.6 across several age groups, while the respective coefficients for neuromuscular performance (maximal strength, or power) have ranged between 0.25 and 0.67 (Ashe et al. 2008, Blain et al. 2001, Calmels et al. 1995, Halle et al. 1990, Henderson et al. 1995, Madsen et al. 1993, Pettersson et al. 1999, Pettersson et al. 1999, Rector et al. 2009, Sandstrom et al. 2000, Sinaki & Offord 1988, Snow-Harter et al. 1990, Taaffe et al. 1995, Taaffe et al. 2001, Taaffe et al. 2001, Taaffe & Marcus 2004, Witzke & Snow 1999, Witzke & Snow 1999, Zimmermann et al. 1990). In regression models, adding neuromuscular performance on top of body size (i.e. body weight and/or height) has increased the proportion of variation explained by the model in predicting skeletal rigidity. As expected, in regression models and correlation analyses, the associations have been higher, when the neuromuscular variable has been functionally related to the bone site of interest (Ashe et al. 2008, Blain et al. 2001, Henderson et al. 1995, Madsen et al. 1993, Nikander et al. 2006, Snow-Harter et al. 1990, Taaffe et al. 1995, Taaffe et al. 2001, Witzke & Snow 1999). Interestingly, the associations between neuromuscular performance and skeletal rigidity have been lower in athlete groups than in sedentary referents (Alfredson et al. 1997, Pettersson et al. 1999, Taaffe & Marcus 2004). Another finding of notice is from Taaffe et al (2001) from a population based study with 2619 healthy older adults in which the lower limb skeletal rigidity was more closely related to knee extension force than femoral neck bone mineral density (Taaffe et al. 2001), indicating that the muscle is not necessarily mostly loading the bone adjacent to it but rather loading the bone, which it is moving.

The effects of aging on the relationship between muscle and bone has been studied by calculating the skeletal rigidity to body mass (Capozza et al. 2004, Ferretti et al. 1998, Ferretti et al. 2003, Melton et al. 2006) or lean body mass ratios (Ferretti et al. 1998, Ferretti et al. 2003, Melton et al. 2006) in different age groups. The bone to body mass ratio has been seen to either decrease or remain stable with aging (Capozza et al. 2004, Ferretti et al. 1998, Ferretti et al. 2003, Melton et al. 2006), whereas the bone to lean body mass ratio has either remained stable or increased slightly with increasing age (Ferretti et al. 1998, Ferretti et al. 2003, Melton et al. 2006).

6 SUMMARY OF THE LITERATURE

Dynamic performance capacity plays a dual role in preventing falls and ensuing bone fractures, by having a positive influence on postural balance (Runge et al. 2004) and skeletal rigidity (Ashe et al. 2008). Dynamic performance, however, is especially affected by aging (Clark & Manini 2008). While general rules for skeletal adaptation to loading have been unveiled (Turner 1998, Turner & Robling 2003, Whalen et al. 1988), it appears that the association between bone loading and skeletal rigidity may depend on age and sex (Capozza et al. 2004, Melton et al. 2006). The analyses of bone muscle interplay have shown that neuromuscular performance is associated with skeletal rigidity and that neuromuscular performance increases the variation explained beyond that of body mass (Ashe et al. 2008, Blain et al. 2001, Calmels et al. 1995, Capozza et al. 2004, Halle et al. 1990, Henderson et al. 1995, Madsen et al. 1993, Pettersson et al. 1999, Sandstrom et al. 2000, Sinaki & Offord 1988, Snow-Harter et al. 1990, Taaffe et al. 1995, Taaffe et al. 2001, Taaffe & Marcus 2004, Witzke & Snow 1999, Zimmermann et al. 1990). However, the change in bone mechanosensitivity with aging (Bassey et al. 1998, Kohrt 2001, Lanyon & Skerry 2001, Rubin et al. 1992, Suominen 2006) has not been unequivocally reflected in the analyses of the effect of aging on the bone muscle interplay. The relationship between skeletal rigidity and loading indices have eiher increased (Melton et al. 2006), remained the same (Ferretti et al. 1998, Ferretti et al. 2003) or decreased (Capozza et al. 2004) with aging.

7 PURPOSE

The purpose of this thesis was to study the associations between body mass, neuromuscular performance and skeletal rigidity in both genders and in young and elderly subjects. This information is expected to facilitate more efficient design of exercise interventions against bone fragility. More specifically the research questions were:

1) Can a relationship be established between ground reaction force and tibial strains? (study I)
2) Is neuromuscular performance a better indicator of skeletal rigidity/loading than body mass or muscle mass? (studies II and III)
3) Does mechanosensitivity change with aging? (studies IV and V)
4) Are habitual explosive actions sufficient to maintain bone health in elderly individuals? (study V)

8 METHODS

A series of five studies was conducted in the process of preparing the present thesis. Convenience samples were recruited for all five studies, where volunteers meeting the inclusion criteria were included as subjects. A total of 241 premenopausal young women, 21 young men, 82 postmenopausal women and 45 elderly men participated in the studies. Table 2 shows the descriptive characteristics of the subjects.

TABLE 2 Descriptive characteristics (mean, SD) of the subjects in different studies.

	Study I			Study II		Study IV	Study V	
	Men	Women	Combined	Premenopausal	Postmenopausal	Elderly men	Volleyball	Control
	N = 20	N= 20	N = 40	N = 221	N = 82	N = 25	N = 10	N = 10
Age [yrs]	24 (2)	24 (3)	24 (3)	23 (5)	58 (4)	72 (4)	70 (4)	70 (4)
Height [cm]	178 (6)	165 (7)	172 (9)	168 (7)	163 (6)	172 (5)	175 (4)	174 (5)
Mass [kg]	77 (11)	62 (9)	69 (13)	63 (9)	72 (11)	75 (9)	78 (7)	81 (9)
BMI [index]	24 (3)	23 (2)	23 (3)	22 (3)	27 (4)	26 (3)	26 (2)	27 (3)
Activity level [times/week]	4 (3)	4 (2)	4 (3)	NA	NA	4 (2)	4 (2)	4 (1)

Inclusion criteria for young subjects (studies I, II and III) were: healthy with no history of lower limb fractures and between 18 and 35 years of age. For the post-menopausal women (study II) inclusion criteria were: early osteoarthritis of grade 1 or 2 on the radiographic Kellgren/Lawrence (K/L) scale in either or both knees. The mean K/L grade was 1.2 (0.9). Postmenopausal subjects engaging in vigorous physical activity more than twice a week were excluded (study

II). In case of elderly men (studies IV and V) the subjects needed to be healthy and their participation in the study was approved by a medical doctor. The volleyball players were measured first and matching controls in terms of age, height and weight were subsequently recruited (study V). On the average the volleyball players had a history of 35 (12) years of habitual volleyball and participated in playing volleyball 3 (1) times/week on the time of measurements. All of the studies were conducted in agreement with the Helsinki declaration with the approval of the University of Jyväskylä ethical committee. Written informed consent was obtained from all participants.

8.1 Bone structural characteristics assessments

Peripheral quantitative computed tomography (pQCT, XCT 3000 (study II postmenopausal women) and XCT 2000 (all other subjects), Stratec Medizintechnik GmbH, Pforzheim, Germany) were performed at the distal tibia (d, 5% of the tibial length proximal to the distal end plate) (studies I, II, IV and IV) and at the tibial mid-shaft (50, 50% of the tibial length proximal to the distal end plate) (all studies) of the right leg. The distal end plate (ankle joint line) was identified from the scout view of the distal tibia. Tibia length (lt) was measured from anatomical landmarks (from knee joint line to medial malleolus) with a tape measure. Total area (ToA), cortical area (CoA), total density (ToD), cortical density (CoD), the distance of the most anterior point from the bending axis corresponding to the maximal cross-sectional moment of inertia (y), density weighted cortical maximal moment of inertia (Imax), maximal section modulus (Zmax) and maximal density weighted section modulus (SSImax) were analyzed from the cross-sectional pQCT-images. A threshold value of 169 mg/cm^3 was used to differentiate trabecular bone from soft tissues (Kontulainen et al. 2007), and 550 mg/cm^3 to differentiate cortical bone from trabecular bone and soft tissues (in accordance with (Hangartner 2007)). Dual energy x-ray absorptiometry (DXA) (Lunar Prodigy, GE Healthcare, USA) was performed at femoral neck (FN) from the right leg of the subject (study V). Areal bone mineral density (aBMD$_{FN}$) and area covered by bone mineral (CSA$_{FN}$) were calculated from the DXA scan.

Bone strength indices were estimated for compressive loading (BSId calculated as the total density (ToDd) squared multiplied by the total area (ToAd)) at the distal tibia and for bending loading (SSImax50 density weighted section modulus or Imax) at the tibial mid-shaft. The SSImax50 was calculated as:

Equation 3 $\sum_{i=1}^{n} \frac{y_i^{2} * D_i * a}{y \max_{50} 1200 \,{}^{mg}\!/_{cm^3}}$

n = number of pixels, i = index of pixel, Di = density of the ith pixel, a = area of pixel, and yi = distance of the ith pixel from the bending axis corresponding to the maximal cross-sectional moment of inertia. Areal bone mineral density was used as an indication of femoral neck rigidity. The in vivo root mean square coefficients of variation (CVRMS) for bone structural variables ranged from 0.4 (for ToDd) to 1.6% (for cross-sectional moment of inertia) and a coefficient of variation of 0.8% has been reported for aBMDFN (Sievänen et al. 1996b).

The CT-image analysis was conducted with Geanie (Commit Ltd., Espoo, Finland) analysis program (studies I, II and V) or using a custom made Matlab (MATLAB® the language of technical computing, version 7.0.1.24704 (R14) service pack 1, The MathWorks, Inc.) script (studies III, IV and V). The validity of the Matlab script was verified by analyzing density weighted polar section modulus from the images and comparing the results against the results obtained form XCT 5.50 (Stratec Medizintechnik GmbH, Pforzheim, Germany) bone analysis software. The r^2 was 0.993 for linear fit (y = 1.0074x+23.753, RMSE = 51.4 mg/cm3).

8.2 Evaluation of neuromuscular performance

8.2.1 Continuous bilateral rebound hopping with extended knees and hips

Before the jumping test, the subjects were asked to warm up with a bicycle ergometer at a freely chosen intensity. Subjects were then instructed to perform bilateral jumping on the soles of the feet using the plantarflexor muscles, keeping the hips and knees extended. The subjects were allowed to familiarize themselves by performing a few sub-maximal jumping trials. The subjects were asked to begin jumping at a low intensity, and gradually increase the intensity to maximal jumping height within 10 – 15 jumps. Knee and hip angles were controlled visually during jumping, and the subjects were continuously given verbal instructions to jump with extended knees and hips, and to avoid ground contact with their heels. Maximal performance was determined from two to four maximal jump efforts on a force plate (Neuromuscular Research Center, University of Jyväskylä, Finland). The effort was accepted as maximal if the two highest vertical GRF peaks from different contacts were within 95% of each other. Three jumps with the highest vertical GRFs were selected for analysis, and the average of those three is reported. Any jump performances with obvious heel contact were excluded from the analysis (FIGURE 7).

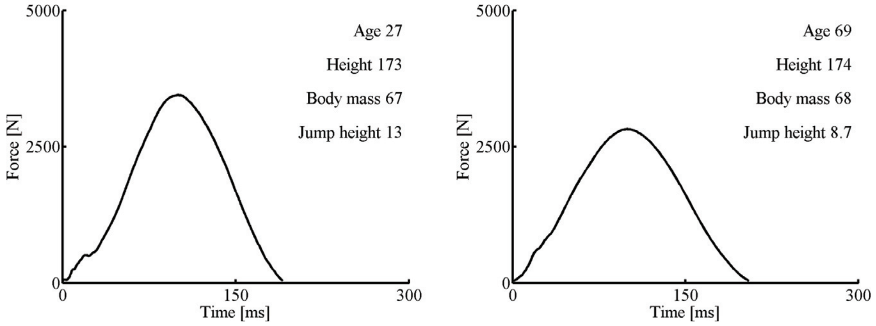


FIGURE 7 Representative examples of vertical ground reaction force of a single ground c ontact from young and elderly men.

The GRF signals were recorded at a sampling frequency of 1000 Hz. A CVRMS of 6.8% was observed for measuring maximal GRF in bilateral hopping for young subjects, and a CVRMS of 5.6% was measured for maximal GRF for elderly subject.

The measured GRFs were low pass filtered at 20 Hz using a 2nd order Butterworth filter. Maximal ground reaction force was defined as the difference between the highest value and the average value, while the subject was in the air (study II). Maximal power was extracted from the ground reaction force curve following the principles reported by Runge et al. (2004). The landing velocity from the preceding jump was calculated as flight time divided by two (i.e. fall time) multiplied by gravitational acceleration (Earth's gravity 9.81 m/s^2). Thereafter, the instantaneous vertical velocity (vi) was calculated as follows:

Equation 4 $v_i = \sum_{n=1}^{i} a_n dt - v_0$,

where i = index of the discrete time point of interest, an = the value of acceleration at the discrete data point n from the beginning of ground contact until the time point of interest, dt = the sampling interval (1 ms), v0 = landing velocity. Instantaneous power was then calculated as the product of the corresponding instantaneous force (including body weight) and velocity. Peak instantaneous power was used to represent maximal power production in bilateral jumping (study IV). Ground reaction force analysis was conducted with Matlab® (MATLAB® the language of technical computing, version 7.0.1.24704 (R14) service pack 1, The MathWorks, Inc., Natick, MA) software. Specific tension during dynamic activity was estimated as maximal GRF divided by the estimated muscle volume.

8.2.2 Counter movement jump

Subjects were asked to perform a counter movement jump on a force platform with hands on the hips. Subjects were instructed to jump as high as possible with the preferred counter movement depth and velocity. A commercial force plate (Kistler Ergojump 1.04, Kistler Instrumente AG,Winterthur, Switzerland) was used for the premenopausal group (study III) and a custom made force plate (University of Jyväskylä, Finland) was used for the postmenopausal women (study III) and elderly men (study V). Vertical ground reaction force was recorded during the whole performance at a sampling frequency of 500 (study III) or 1000 Hz (FIGURE 8) (study V).

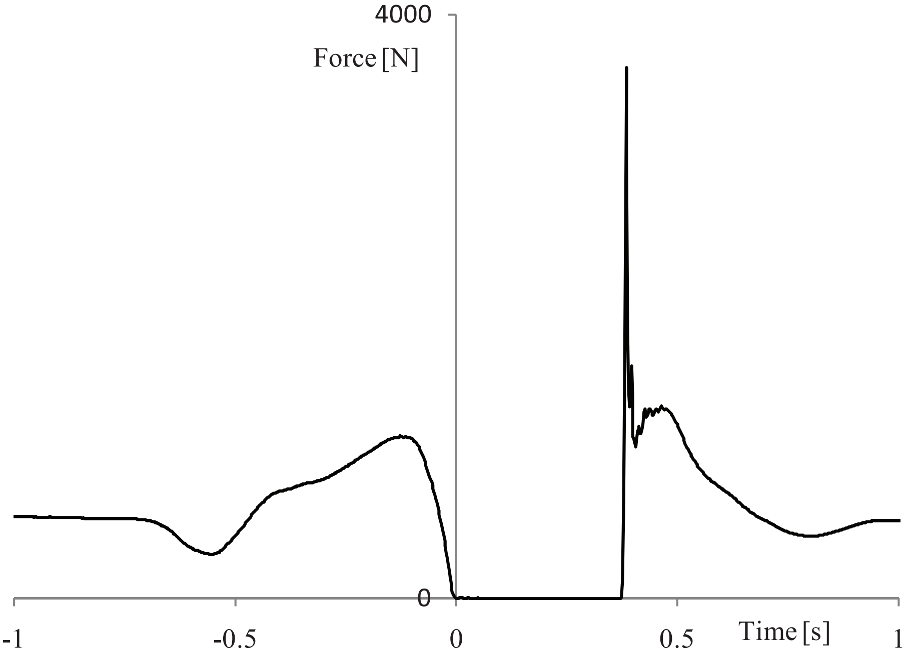


FIGURE 8 A representative example of vertical ground reaction force in counter movement jump from a premenopausal woman.

As potential indices of bone loading concentric net impulse and peak power during the take-off phase were analyzed from the vertical ground reaction force using a custom made Matlab script. Maximal power was extracted from the ground reaction force curve following the methodology reported by Runge et al. (2004). Briefly, the weight of the subject was subtracted from the recorded vertical ground reaction force and then divided by the body mass of the subject to produce vertical acceleration. Thereafter, instantaneous vertical velocity of the center of mass was calculated as the sum of acceleration data points multiplied by the inverse of sampling frequency from the beginning of the counter movement until the corresponding time point. Instantaneous power was then calculated as the product of the corresponding instantaneous force (including body weight) and velocity values. Peak instantaneous power was selected to represent power production of the lower body musculature. Concentric net impulse was calculated as the integral of the vertical ground reaction force minus the gravitational force caused by body weight from the beginning of the counter movement to the instant of take-off. Coefficients of variation of 3 – 4% have been reported for measuring jump height (Torvinen et al. 2002) and power (Rittweger et al. 2004) in counter movement jumping.

8.2.3 Maximal voluntary ankle extension torque measurement

The maximum isometric and eccentric muscle torque was measured with custom made dynamometer (Nicol et al. 1996) during unilateral ankle plantarflexion with knee extended. The subject was sitting comfortably with the upper body in an angle of 110° compared to the legs. The legs were in parallel with the floor. Isometric torque was measured at various angles with 5° increments beginning from approximately 80° between the sole of the foot and tibia and finishing at approximately 105°. Torque angle relationship was determined from the isometric maximal voluntary contractions (MVC). The subjects were exhorted verbally to ensure maximal effort. The angle of the highest isometric torque value was selected as the optimal angle. Eccentric contractions were measured isokinetically at an angular velocity of 20 °/s. The angular displacement started from 115°. The eccentric torque was measured at an optimal angle. The CVRMS ranged from 5.6 to 10.2% for the maximal voluntary torque measurements.

8.2.4 Maximal voluntary leg extension force

The maximum bilateral leg extension force was measured on a custom made leg extension dynamometer (University of Jyväskylä, Finland). The measurement was conducted in a seated position. Upper body was approximately at a 110° angle from the horizontal plane, knee angle was set at 90° using a goniometer. The force plate was directly in front of the subject. The force plate was allowed to rotate slightly around the vertical plane to allow for possible anatomical constraints of the subjects' ankle range of motion so that the sole of the foot was firmly against the force plate. The maximal force was determined as the difference between the maximal measured force and the force level when the subject was resting feet relaxed against the force plate. One control subject was unable to perform the leg extension test and therefore the N=9 for the control group in study V.

8.2.5 Muscle volume estimation

The volume of the ankle plantar-flexor muscle group was estimated from muscle thickness and limb length (Miyatani et al. 2004). The limb length was determined as the length between knee joint line at the lateral side and the lateral malleolus of tibia.

Muscle thickness was obtained from a cross-sectional image of the ankle plantar flexor muscle group with ultrasonographic measurement device (Prosound SSD-5500, Aloka, Tokyo, Japan). The thickest part of the muscle was used in the determination of muscle thickness. Muscle thickness was measured online from still captured ultrasound picture. CVRMS was 10% for the volume estimation. The volume of the plantar flexors was estimated from the thickness and limb length as follows (Miyatani et al. 2004):

Equation 5 $\text{Muscle volume [cm3]} = 218.1 * \text{Thickness} + 30.7 * \text{Limb length} – 1730.4$

8.2.6 Specific tension estimation

Relative specific tension was estimated from the ankle plantar flexor muscles. The specific tension was calculated as maximum voluntary torque produced divided by muscle volume as suggested by Fukunaga et al. (2001):

Equation 6 $TQ = MV * ST * MA / FL * \cos\theta$

where TQ = torque, MV = muscle volume, ST = specific tension, MA = moment arm, FL = fiber length and θ = pennation angle. If MA to FL ratio is assumed to be constant among subjects and the effect of pennation angle changes on muscle force is assumed to be negligible (Fukunaga et al. 2001) it follows that (Lynch et al. 1999)

Equation 7 $ST = TQ / MV$ [N/m3]

8.2.7 Voluntary activation measurement

Voluntary activation was measured during eccentric maximal voluntary contraction from the ankle plantar flexor muscles using superimposed twitch method (Kent-Braun & Le Blanc 1996, Merton 1954). The level of activation was calculated with the activation level (AL) equation (Babault et al. 2001).

Equation 8 $AL = (1 – \text{Superimposed burst torque}/\text{Burst torque at rest})\cdot 100$

The AL was measured at an angle corresponding to optimal angle in isometric contraction during maximal eccentric ankle plantar flexor actions. The CVRMS for the activation level measurement was 4.2%

In the eccentric contraction the torque level with stimulation was defined as the torque during maximal positive difference between the measured torque curve and post-stimulus torque line estimated with linear extrapolation (Allen et al. 1998). The twitch force was defined as the difference between the measured torque and extrapolated torque (Babault et al. 2001).

8.2.8 Electrical Stimulation

Electrical stimulation was conducted to tibial nerve with the stimulation electrode placed over the tibial nerve in the popliteal fossa and the anode (Vtrode neurostimulation electrodes 2*4 inch oval electrode, Mettler electronics, Anaheim, CA, U.S.A.) placed below the patella. The placement of the stimulation electrode was controlled by visually inspecting the twitch response to single stimuli. The placement of the stimulating electrode was accepted when the twitch response was evenly distributed in plantar flexors and minimal twitch response was observed in the tibialis anterior muscle. Once the stimulation site was established with a reusable stimulating electrode a disposable electrode (Unilect short-term Ag/AgCl ECG electrode) was placed on the established stimulation site. Sufficient pressure of the stimulation electrode was applied manually.

A 50 ms submaximal stimulus train at 100 Hz frequency (= 6 stimuli) was applied with electrical stimulator (Digitimer constant current stimulator model DS7A, Digitimer, Welwyn garden city, England). The intensity of stimulation was adjusted to induce in relaxed muscle a twitch response torque of 30 – 40% of previously measured isometric MVC torque. The duration of the current pulse was 200 µs and the maximum voltage was 200 V. In the eccentric activity, the timing of the stimulus was adjusted so that maximal evoked twitch torque occurred at the time corresponding to optimal angle. The advance of the stimulus train application was determined from the twitch evoked to active muscle and was the time from the stimulus trigger to the peak of the evoked force. In practice the stimulus train was applied 50 ms prior to ankle angle reaching the optimum angle.

8.2.9 Osteogenic index in counter movement jump

The measured GRFs were low pass filtered at 20 Hz using a 2nd order Butterworth filter. Maximal power was extracted from the ground reaction force curve following the principles reported by Runge et al. (2004). For the osteogenic index (OI) calculation the ground reaction force was divided by the mass of the subject to produce acceleration curve. The last bell shaped part above zero acceleration was selected for further analysis (FIGURE 9).

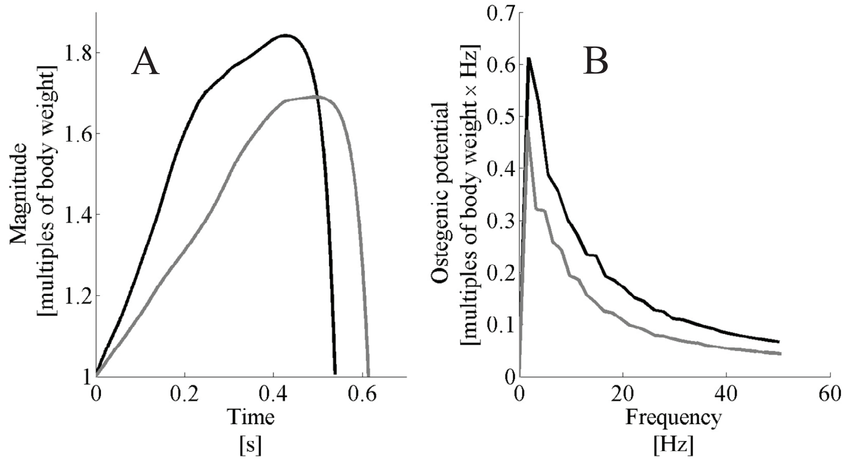


FIGURE 9 Averaged acceleration curves (black = volleyball, grey = control) of the last bell shaped part above gravitational acceleration used for the osteogenic index (OI) calculation. Left pane: averaged acceleration curves, Right pane: Amplitude multiplied by the respective frequency plotted against the frequency of the averaged traces.

The maximal acceleration was selected to represent the magnitude of the signal. A fast Fourier transformation was calculated from the signal and the mean magnitude frequency (MMF) was selected to represent the rate of change of the signal. OI was thereafter calculated as follows (Turner 1998):

Equation 9 $OI = \sum_{i=1}^{f_i \leq 50\,Hz} \varepsilon_i f_i$

where , Ai = i:th cosine coefficient of the Fourier series, Bi = i:th sine coefficient of the Fourier series, fi = i:th frequency in the Fourier series. Frequency content up to 50 Hz was included in the OI analysis. Ground reaction force analysis was conducted with MATLAB® (MATLAB® the language of technical computing, version 7.0.1.24704 (R14) service pack 1, The MathWorks, Inc.) software.

8.3 Modeling tibial strains in walking

A generic lower body musculoskeletal model was built according to several anthropometric variables (gender male, height 184 cm, weight 89 kg, age 25 years and ethnicity caucasian) of the study subject. The subject was asked to perform a walking test on a level surface at constant speed. In order to track the body motion, visual markers were placed on various locations of the subject (FIGURE 10).

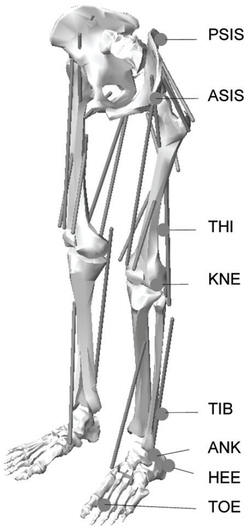


FIGURE 10 Graphical representation of the lower body musculoskeletal model used in the study with schematic illustration of motion capture marker placement. ASIS = anterior superior iliac spine, PSIS = posterior superior iliac spine, KNE = lateral epicondyle of the knee, THI = lower lateral 1/3 surface of the thigh, ANK = lateral malleolus, TIB = lower 1/3 of the shank, TOE = second metatarsal head, HEE = calcaneous at the same height as the toe marker.

The motion capture system (Peak Motus 8.10, Vicon Motion Systems, Inc., Centennial, CO, USA) tracked the markers' trajectories during the walking performance. The trajectories were then used to drive the model in the inverse dynamics simulation where the desired muscles shortening/lengthening patterns were calculated. Within the constraints applied to the model, each muscle replicated the desired shortening/lengthening pattern obtained from the inverse dynamics simulation in the forward dynamics simulation in order to reproduce the motion. This was accomplished through a proportional derivative servo controller which minimized the error between the desired shortening/lengthening pattern and the actual one of each muscle obtained from the forward dynamics simulation. Using the forward dynamics simulation, the lower body model with the flexible tibia was employed to estimate the tibial deformations resulting from walking on a level surface. The deformations were used to define the tibial strains (musculoskeletal model described in further detail in (Al Nazer 2008)).

8.3.1 Motion Capture

The subject was asked to walk barefoot at a constant velocity (1.47 m/s) on top of a 10 m long force platform (Raute Inc., Finland) on level ground. The resultant ground reaction force and electromyographic (EMG) activities of the tibialis anterior, soleus, rectus femoris, vastus lateralis, biceps femoris and gluteus medius muscles were recorded from the right side of the body (Mespec 400 EMG Radio Telemetry System, Mega Lectronics Ltd, Finland). The EMG signals were sampled at 1000 Hz and SENIAM recommendations were followed in placement of electrodes (Hermens et al. 2000) The walking exercise was recorded with four digital video cameras (COHU High Performance CCD Camera, San Diego CA, USA) at a 50 Hz sampling frequency. A schematic illustration of the measurement set up is provided in FIGURE 11.

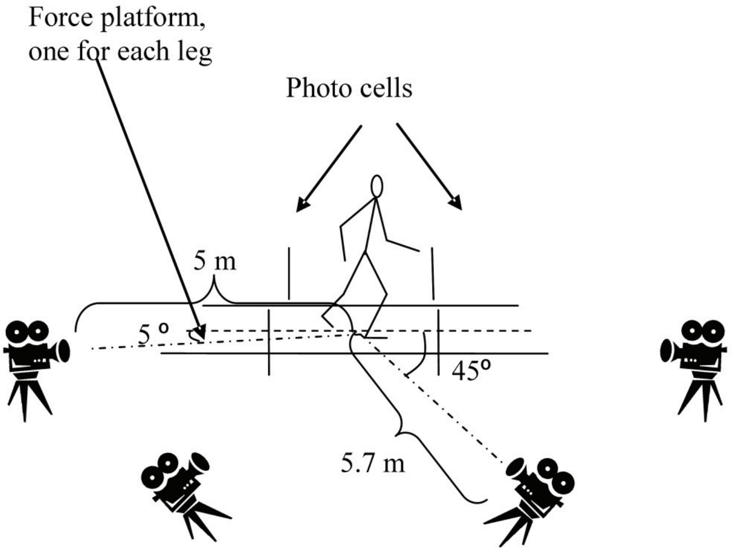


FIGURE 11 Schematic illustration of the experimental set up.

Visual markers were applied on the lower body of the subject, as shown in Figure 10. One stride, from the heel strike of the right leg to the next heel strike, was selected for the analysis. The video clips from all four cameras were digitized using Peak Motus 8.1.0 (Peak Performance Technologies Inc., USA), and the software was used to calculate the three-dimensional coordinates for each marker. In order to minimize the digitization error, each of the coordinates was filtered with a 2nd order 5 Hz low-pass Butterworth filter (Silva & Ambrósio 2002). The coordinates were then interpolated so that coordinate data for a total of four identical walking cycles were produced.

8.3.2 Determining tibial strains

The principal strains and strain rates were obtained from the model at a location corresponding to the location defined by Lanyon (1975), Burr et al. (1996), Milgrom et al. (2000) and Milgrom et al. (2006) at the anteromedial aspect of the right tibial midshaft (Burr et al. 1996, Lanyon et al. 1975, Milgrom et al. 2000b, Milgrom et al. 2007). In order to verify the accuracy of the introduced model, the simulated ground reaction force and muscular forces were compared in terms of the cross-correlation coefficient (γ) to the measured ground reaction force and EMG. Moreover, the model kinematics measured from inverse and forward dynamics simulations were compared in order to verify that the model was capable of replicating the motion in forward dynamics simulation. This was accomplished by comparing the position of the center mass of each segment in the model in the X, Y and Z directions resulting from inverse dynamics simulation to their correspondences resulting from forward dynamics simulation in terms of γ.

8.4 Estimating indices of tibial loading

The ratio of Achilles tendon force to GRF has been found to be 3.47 (Komi et al. 1992), 1.49 (Finni et al. 1998) and 2.0 (Ishikawa et al. 2005a) in *in vivo* walking measurements. Using the mean of these values, the Achilles tendon force was estimated to be 2.3 times GRF under one foot (GRF_{one}), which represents half of the measured peak GRF during maximal bilateral jumping. Achilles tendon moment arm ($R_{Achilles}$) was estimated to be 0.2 times foot length (Giddings et al. 2000), which was estimated to be 0.152 times height (Winter 2005). Axial compressive stress (σ_{c50}) at the tibial mid-shaft was then calculated as the sum of GRF under one foot and Achilles tendon force, divided by cortical area at the tibial mid-shaft:

Equation 10 $$\sigma_{c50} = \frac{3.3 * GRF_{one}}{CoA_{50}}$$

Given the short distance to the ankle joint, the contribution of stress caused by bending to overall compressive stress was assumed to be negligible at the distal tibia. Axial compressive stress at the distal tibia was thus calculated as follows:

Equation 11 $$\sigma_{cd} = \frac{3.3 * GRF_{one}}{ToA_d}$$

To estimate tibial mid-shaft normal tensile stress caused by bending (σ_{b50}), the bending moment was calculated as the estimated Achilles tendon force multiplied by the Achilles tendon moment arm. Stress was then estimated for the most anterior point of the tibial mid-shaft, by dividing the bending moment by the maximal section modulus ($Zmax_{50}$):

Equation 12 $\sigma_{b50} = \frac{2.3 * GRF_{one} * R_{Achilles}}{Z\max_{50}}$

To produce an estimate of the tensile normal stress at the most anterior bone site of the tibial mid-shaft, compressive stress was subtracted from the stress caused by bending. Strain equals stress divided by the elastic modulus of the material. As the elastic modulus of cortical bone is related to the cube of volumetric bone mineral apparent density (Martin 1991), the tensile strain index (ε_{t50}) at the tibial midshaft was calculated as follows:

Equation 13 $\varepsilon_{t50} = \frac{\sigma_{b50} - \sigma_{c50}}{CoD_{50}^3}$

As the elastic modulus of trabecular bone is related to the square of volumetric bone mineral apparent density (Martin 1991), the compressive strain index (ε_{cd}) at the distal tibia was calculated as follows:

Equation 14 $\varepsilon_{cd} = \frac{\sigma_{cd}}{ToD_d^2}$

Besides the estimation of load-induced stress and strain, bone rigidity to loading ratios were calculated by dividing estimated bone strength index (BSId or Zmax$_{50}$) by appropriate indicators of loading (body mass, muscle volume, GRF and peak power).

8.5 Statistical analysis

Mean and standard deviation (SD) are given as descriptive statistics. Normal distribution was analyzed with Shapiro-Wilk normality test. Preliminary statistical power analysis was conducted, which indicated that for 0.8 statistical power an N of 10 in each group is required to detect a difference of 14% when the expected standard deviation of the difference is 10% (study V).

Associations between the independent neuromuscular variables or predictors (body mass, maximal ground reaction force, peak power, impulse torque, specific tension, activation level) and dependent bone robusticity variables or outcomes (ToD, ToA, CoA, BSId, Imax, SSImax, Zmax, aBMDFN, CSAFN) were determined by Pearson product moment correlation (study I and II) and Spearman rank correlation coefficient (study IV). Group comparisons were made with independent t-test (study II), Mann-Whitney U (study IV) or related samples Wilcoxon test (study V). Forced regression models were developed with neuromuscular variables and height and age as the independent variables and bone robusticity variables as the dependent variables (studies I and II). The significance limit was set at $P \leqslant 0.05$ for all statistical analyses. Statistical analyses were conducted with SPSS 13.0.1 (SPSS Inc.) statistical analysis program.

9 RESULTS

9.1 Descriptive characteristics of the subjects

Descpritive characteristics of the subjects are given in Table 2. Young men were 3% taller than elderly men (P = 0.001) (study IV). Elderly volleyball players were 4% lighter than their matched peers (P = 0.041) (study V). Pre- and postmenopausal groups were not compared to each other due to postmenopausal subjects being osteoarthritis patients and the premenopausal subjects being athletes.

9.2 Bone structural characteristics

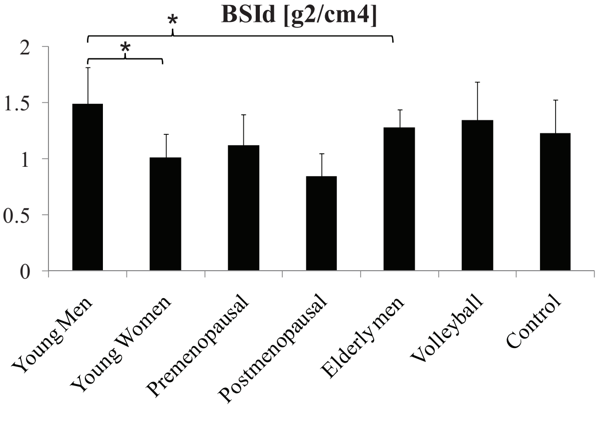


FIGURE 12 Distal tibia compressive bone strength index. An asterisk (*) signifies statisticly significant difference between groups (P < 0.05). Young men were compared to young women and elderly men. Volleyball players were compated to controls.

TABLE 3 Bone structural characteristics (Mean, SD).

	Study I			Study II		Study IV	Study V	
	Men	Women	Combined	Pre menopausal	Post menopausal	Elderly men	Volleyball	Control
	N = 20	N= 20	N = 40	N = 221	N = 82	N = 25	N = 10	N = 10
ToD$_d$ [mg/cm^3]	368 (46)	337 (40)	352 (45)	368 (37)	306 (32)	330 (22)	340 (36)	333 (30)
ToA$_d$ [mm^2]	1110 (170)	892 (88)	999 (172)	819 (137)	899 (142)	1200 (100)	1150 (180)	1100 (130)
ToA$_{50}$ [mm^2]	463 (56)	375 (55)	419 (71)	340 (53)	314 (34)	468 (38)	510 (36)	479 (39)
I$_{max50}$ [mm^4]	29600 (7300)	19400 (5800)	24500 (8300)	26200 (7700)	21600 (5300)	31200 (6200)	35200 (6900)	31900 (6800)
dwI-max$_{50}$ [mg cm]	3350 (780)	2190 (620)	2770 (910)	2900 (840)	2350 (580)	3430 (670)	3900 (770)	3560 (750)

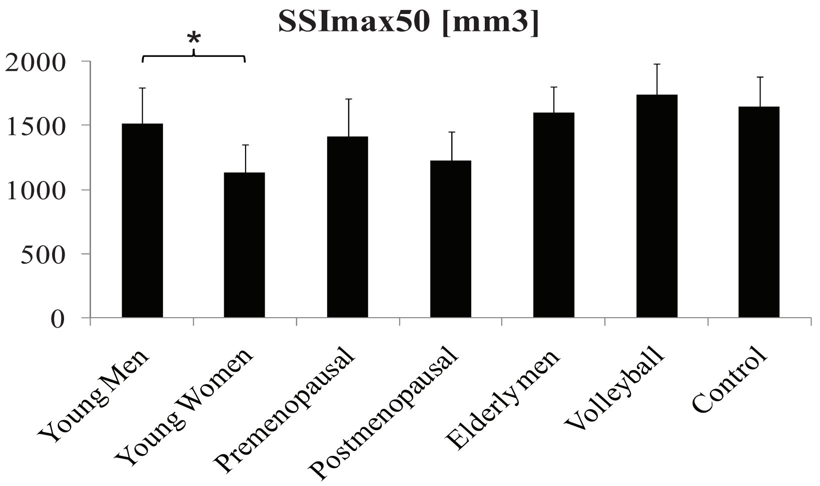


FIGURE 13 Tibial mid-shaft bending strength index. An asterisk (*) signifies statistically significant difference between groups ($P < 0.05$). Young men were compared to young women and elderly men. Volleyball players were compated to controls.

Bone structural characteristics are given in TABLE 3, FIGURE 12 and FIGURE 13.

9.3 Neuromuscular performance

TABLE 4 Neuromuscular performance in continuous bilateral rebound hopping.

	Study I Men N = 20	Study IV Elderly men N = 25
Maximal GRF (hopping) [N]	4680 (1020)	3080 (600)
Jump height (hopping) [cm]	19.9 (8.7)	8.7 (3.7)
Contact time [ms]	180 (24)	226 (41)
Power (hopping) [W]	4680 (1280)	2530 (740)
Tensile stress [MPa]	144 (23)	94 (21)
Compressive strain [index]	0.484 (0.102)	0.399 (0.078)
Tensile strain [index]	0.107 (0.016)	0.071 (0.018)

Young men produced higher maximal GRF in hopping (4680 (1020) vs. 3570 (710) N), had higher maximal voluntary eccentric ankle plantarflexion torque (277 (51) vs. 201 (32) Nm) and larger muscle volume (1000 (150) vs. 730 (160) cm3) than young women (P < 0.05) (study I). There were no differences in specific tension (0.280 (0.052) vs. 0.291 (0.064) Nm/cm3) or activation level in maximal eccentric ankle plantarflexion between young men and women (P > 0.05). Young men had larger muscle volume (1000 (150) vs. 850 (141) cm3), 38% higher maximal GRF, higher specific tension (4.71 (1.05) vs. 3.71 (1.11) N/cm3), larger impulse (149 (32) vs. 100 (25) Ns), 128% higher jump height, 20% shorter contact time, 85% higher maximal power, 53% higher tensile stress and 50% higher strain indices in hopping than the elderly men (P < 0.05) (
TABLE 4) (study IV).

TABLE 5 Neuromuscular performance in counter movement jump.

	Study II		Study V	
	Premenopausal	Postmenopausal	Volleyball	Control
	N = 221	N = 82	N = 10	N = 10
Impulse [Ns]	143 (25)	113 (21)	152 (26)	136 (24)
Jump height [cm]	27 (6.1)	13.1 (3.3)	19.4 (5.4)	14.3 (2.8)
Power [W]	2660 (550)	1870 (360)	2570 (450)	2180 (410)

Performance results from counter movement jump test for pre- and postmenopausal women are given in TABLE 5. Elderly volleyball players had 13% larger impulse, 37% higher jump height, 19% peak power, higher magnitude (1.02 (0.21) vs. 0.76 (0.13)g) and higher osteogenic index (5.5 (1.06) vs. 4.09 (0.70) index) in CMJ than their matched peers (P < 0.05) (Table 5). No difference was observed in maximal voluntary eccentric ankle plantarflexion torque (243 (29) vs. 244 (42) Nm), leg extension force (160 (48) vs. 154 (22) kg) or the mean magnitude frequency (3.88 (0.29) vs. 3.70 (0.34) Hz) ($P > 0.05$) (study V).

9.4 Associations between neuromuscular performance and indices of skeletal rigidity

Positive correlation between body mass and net concentric impulse was observed among young men ($r = 0.64$) and women ($r = 0.71$) (study I), pre- ($r = 0.75$) and postmenopausal ($r = 0.68$) women (study II) ($P < 0.05$). Moderate positive associations were observed between net concentric impulse and bone strength indices (BSId, dwImax50) among young men ($r = 0.59 – 0.61$) (study I), pre- ($r = 0.47 – 0.54$) and postmenopausal women ($r = 0.48 – 0.53$) (study II) ($P < 0.05$). Generally higher correlations were seen between impulse and indices of bone strength (mean for studies I,II,IV and V BSId $r = 0.40$, range 0.26 to 0.59, dwImax50 $r = 0.49$, range 0.24 to 0.71) than between body mass and bone strength (mean for studies I,II,IV and V BSId $r = 0.26$, range 0.08 to 0.42, dwImax50 $r = 0.35$, range 0.08 to 0.63) (FIGURE 14).

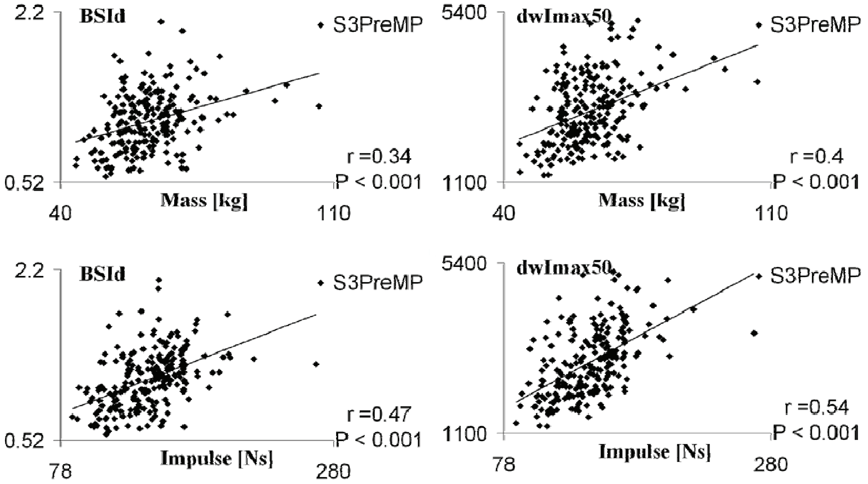


FIGURE 14 Associations between body mass or impulse in CMJ and bone strength indices (compressive and bending strength indexes). Example from the premenopausal group from study II.

9.5 Regression models predicting skeletal rigidity

Between 14 to 36% of the variation in distal tibia compressive bone strength index was explained by body size (represented by height & body mass), whereas the predictive power of the model was increased by 2 – 7%, when neuromuscular performance was included into the model as an independent variable (TABLE 6 and TABLE 7) (studies I and II). 25 to 60% of the variation in tibial mid-shaft bending strength (represented by SSImax50) was explained by body size, whereas the predictive power of the model was increased by 6 – 12%, when neuromuscular performance was included into the model as an independent variable (studies I and II). Body mass became a non-significant predictor of skeletal rigidity, when neuromuscular performance was accounted for by other predictor variables.

TABLE 6 Regression results for young men and women combined (study I). Percentages of variation explained and the total amount of variation explained by the model. BSId = distal tibia compressive bone strength index, SSImax50 = Density weighted section modulus at tibial mid-shaft. The increment of explanatory power with the inclusion of a given independent variable is highlighted with an asterisk if the added variable had significant independent ($^* P \leqslant 0.05$) explanatory effect. An asterisk signifies that the explanatory power of the model reached significance ($^* P \leqslant 0.05$).

	BSI_d	SSImax_{50}
N = 40		
Height & Body mass	37.6	**59.4***
Muscle volume	1.3	**4.2***
Specific tension	3.1	**4.3***
Activation level	3.7	0.4
TOTAL	**45.8***	**68.3***
N = 40		
Muscle volume	**35.7***	**60.4***
Specific tension (ankle plantarflexion)	4.8	**6.0***
Activation level	3.2	0.1
TOTAL	**43.7***	**66.5***

TABLE 7 Regression coefficients (β) and the amounts of variation explained (R2) by the regression models at the distal tibia (BSId) and tibial midshaft (SSImax50) for pre- and postmenopausal women (study II). Height, body mass and age were included in the model in the first step, and impulse was entered in the second step.

BSI_d [g^2/cm^4]	PreMP		PostMP	
	β (P-value)	R^2 (P-value)	β (P-value)	R^2 (P-value)
Step 1				
Constant	-0.480 (P = 0.291)		0.934 (P = 0.189)	
Height [cm]	0.00595 (P = 0.037)	0.14 (P < 0.001)	0.000222 (P = 0.956)	0.16 (P = 0.004)
Body mass [kg]	0.00853 (P < 0.001)		0.00559 (P = 0.015)	
Age [yrs]	0.00273 (P = 0.479)		-0.00911 (P = 0.085)	
Step 2				
Constant	-0.205 (P = 0.635)		0.712 (P = 0.299)	
Height [cm]	0.00359 (P = 0.19)		-0.00161 (P = 0.678)	
Body mass [kg]	-0.00134 (P = 0.649)	0.16 (P = 0.004)	0.0013 (P = 0.625)	0.23 (P < 0.001)
Age [yrs]	0.00323 (P = 0.378)		-0.0027 (P = 0.626)	
Impulse [Ns]	0.00510 (P < 0.001)		0.00404 (P = 0.007)	
$SSImax_{50}$ [mm^3]				
Step 1				
Constant	-2190 (P < 0.001)		-1310 (P = 0.073)	
Height [cm]	17.8 (P < 0.001)	0.32 (P < 0.001)	14.4 (P < 0.001)	0.25 (P < 0.001)
Body mass [kg]	6.62 (P = 0.002)		3.62 (P = 0.118)	
Age [yrs]	8.37 (P = 0.020)		-1.12 (P = 0.835)	
Step 2				
Constant	-1920 (P < 0.001)		-1620 (P = 0.018)	
Height [cm]	15.4 (P < 0.001)		11.9 (P = 0.002)	
Body mass [kg]	-3.26 (P = 0.229)	0.40 (P < 0.001)	-2.31 (P = 0.377)	0.37 (P < 0.001)
Age [yrs]	8.86 (P = 0.009)		7.75 (P = 0.156)	
Impulse [Ns]	5.1 (P < 0.001)		5.58 (P < 0.001)	

9.6 Tibial strains in walking

The cross-correlation coefficient (γ) between measured and simulated ground reaction force values was 0.97. As for the muscular forces, a γ of 0.94 was obtained for the soleus, 0.75 for the gluteus medius, 0.65 for the vastus lateralis, 0.39 for the tibialis anterior, 0.33 for the biceps femoris and 0.22 for the rectus femoris. In the comparison of the model kinematics between inverse and forward dynamics simulations, the γ was higher than 0.99 for the position of the center mass of each segment in the model in the X, Y and Z directions.
FIGURE 15 shows the simulated maximum and minimum principal strains for four walking cycles. The numerical maximum and minimum strain magnitudes and rates are given in TABLE 6.

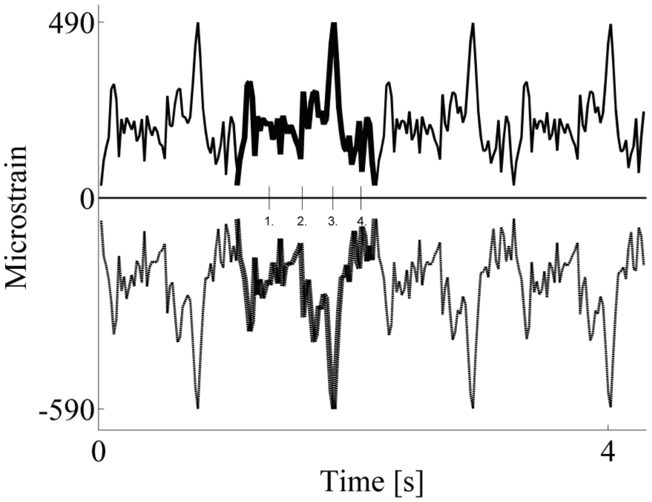


FIGURE 15 Maximum (solid line -) and minimum (dotted line - -) principal strain curves for four walking cycles. Points 1-4 correspond to the four distinct inflections during one walking cycle defined by Lanyon et al. (1975), which are 1) heel strike, 2) full foot-heel off, 3) heel off-toe off and 4) forward swing.

TABLE 6 The principal strain magnitudes and rates. Literature values from in vivo measurements and the values estimated by the model. The principal strains and strain rates were obtained from the model at the anteromedial aspect of the right tibial midshaft, which is the same location in all of the studies mentioned in the table.

	Principal Strain Magnitude [microstrain]		Strain rate [microstrain/s]	
	Maximum	Minimum	Maximum	Minimum
(Lanyon et al. 1975)	395	-434	Not reported	-4000
(Burr et al. 1996)	437	-544	11006	-7183
(Milgrom et al. 2000b)	840	-454	3955	-3306
(Milgrom et al. 2007)	394	-672	4683	-3820
Simulation results	490	-588	3800	-4100

10 DISCUSSION

The primary finding of the present thesis was that in adults irrespective of age and gender, skeletal rigidity is more closely related to neuromuscular performance than to body mass. However, the association between neuromuscular performance and skeletal rigidity seems to be age dependent. Moreover, the sensitivity to loading may change with aging as indicated by the lower values in bone stress and strain indices among elderly men compared to young men. Furthermore, in all age groups, including performance in regression models predicting the skeletal rigidity increased the explanatory power of the model. Moreover, within age group, the subject groups with differing skeletal structure could be differentiated from each other according to neuromuscular performance.

10.1 Association between neuromuscular performance and bone strength indices

In line with literature (Ashe et al. 2008, Blain et al. 2001, Calmels et al. 1995, Halle et al. 1990, Madsen et al. 1993, Pettersson et al. 1999, Sandstrom et al. 2000, Sinaki & Offord 1988, Snow-Harter et al. 1990, Taaffe et al. 1995, Taaffe et al. 2001, Taaffe & Marcus 2004, Witzke & Snow 1999, Zimmermann et al. 1990), it was seen in the present results that in young adults muscle volume, maximal voluntary eccentric torque, maximal ground reaction force in jumping and specific tension were significantly related to bone structural characteristics. When looking at the pre- and postmenopausal women the primary findings were that 1) variation in body mass became a non-significant predictor of tibial bone strength when a proper index of neuromuscular performance was included in the regression model as a predictor. 2) The associations between loading indices (body mass, impulse) and bone strength indices ($dwImax_{50}$, BSI_d) were similar among athletic premenopausal women representing higher skeletal loading and osteoarthritic postmenopausal women representing lower skeletal loading. In comparing the young men to the elderly men it was found that young men were able to load their bones to a greater extent than elderly men in a similar jumping exercise. This was exemplified by lower tibial rigidity to neuromuscular performance ratio than in the elderly subjects, which may reflect some kind of age related dissociation in bone adaptation to loading. Finally, while comparing habitual male volleyball players to their matched peers it was seen that habitual elderly male volleyball players were able to produce higher osteogenic index in maximal counter movement jump performance than their body-size and age matched controls. In addition, the habitual volleyball players had superior performance in counter movement jump and had larger cross-sectional area at tibial mid-shaft than their age and body-size matched controls.

10.1.1 Age effects

Young men were able to load their bones to a greater extent than elderly men in a similar jumping exercise. This was exemplified by lower bone rigidity to neuromuscular performance ratio than in elderly subjects, which may reflect some kind of age related dissociation in bone adaptation to loading. Melton et al. (2006) recently reported similar results, showing an increased ratio of femoral neck bending strength index to estimated leg muscle volume with increasing age but no change in the respective ratio to body weight, both in men and women. Calmels et al. (1995) reported similar observations in women. All of these findings are in line with the argument that bone loss lags behind the decline in physical performance in aging (Frost 1997a). An alternative explanation for these findings is that the set point of the Mechanostat (Frost 2003) could become lower with age, i.e. the elderly would require less loading than the young in order for their bones to reach similar relative bone rigidity. If this were the case, one would expect to see a similar association between bone and performance in both age groups, which evidently was not the case.

In line with the rationale proposed by Frost (Frost 1997a), the older group had a higher ratio of bone rigidity to loading, which was particularly evident when the loading was estimated based on neuromuscular performance. Given the adaptation of bone to prevalent loading, bone loss should follow, but lag behind, the decline in physical performance with aging. Assuming a two year delay and a 3.5% annual decline in muscular power (Barry & Carson 2004) as a reasonable indicator of the change in dynamic physical performance after 60 years of age, a 7.4% increase in bone to loading ratio would be expected (the effect of mere performance decline on the ratio is calculated as $1/0.965^2$, which equals 1.074). However, even if the lower border of the 95% confidence interval of the maximal GRF to Z_{max50} ratio was considered, the ratio was still 31% higher in the elderly than in the young subjects. Thus, a difference of this magnitude cannot be explained merely by the lag in bone adaptation as suggested by Frost (Frost 1997a). Regarding the validity of a two-year delay, even a time lag as short as one month between decreased activity and the beginning of observable bone loss has been reported in bed rest studies (Rittweger & Felsenberg 2003, Rittweger et al. 2005).

For the distal tibia, it may be argued that the difference between young and elderly men was approximately what could be expected by the two year delay in bone adaptation used for the calculations. The lower limit of the confidence interval of the maximal GRF to BSI_d ratio indicated 5.7% higher values for the elderly than for the young subjects. More marked changes in trabecular volumetric bone mineral density (vBMD) than cortical vBMD have been observed in men during aging (Riggs et al. 2004). Therefore, it cannot be ruled out that the tibial midshaft, consisting primarily of cortical bone, is simply metabolically too slow to remove the surplus bone material, or is unable to reduce its cross-sectional size, which mainly accounts for the rigidity of the given site. In fact, the results from patients with spinal cord injury (Eser et al. 2004a) support this suggestion. After paralysis caused by spinal cord injury, changes in bone rigidity at the tibial midshaft are smaller than the respective changes at the distal tibia (Eser et al. 2004a).

Mechanical properties of cortical bone change little with aging. Zioupos & Currey (1998) showed a decrease of about 15% in elastic (Young's) modulus with aging in femoral cortical bone, whereas no such change was seen by Burstein et al. (1976). Load-induced strains within the bone, the apparent key players in mechanotransduction (Riddle & Donahue 2008, Scott et al. 2008), would be similar with equal loading (relative to bone size and geometry) with Young's modulus and material composition remaining the same during aging. While the long bones of the elderly may have similar flexural rigidity (the product of Young's modulus and cross-sectional moment of inertia) to those of young subjects, they also have thinner cortices and wider outer diameters (Riggs et al. 2004). This would mean that similar loading would actually cause greater strains in the elderly bone. Furthermore, increasing porosity of cortical bone to the order of 10% (indicated by lower apparent BMD measured with pQCT) has been observed with aging in tibial cortical bone from twenty to ninety years of age (Riggs et al. 2004), which would further accentuate strains in the elderly bone by decreasing bone stiffness. In the present thesis, these phenomena were accounted for by the tensile strain index, which revealed that young subjects were able to produce a 51% higher strain index than the elderly in the bilateral jumping test, primarily because of the substantially superior physical performance of the young men. Therefore, as also concluded by Melton et al. (2006), there is an increase in the bone to loading ratio at the tibial midshaft, which may not be accounted for by the Mechanostat hypothesis (Frost 2003). Neither can the difference in bone to loading ratio be explained by small age-related changes in bone elastic properties or the above discussed delay in bone adaptation. There are several possible explanations which could at least partly account for the observed difference between young and elderly subjects. Firstly, bone mechanosensitivity may have decreased, which has been suggested to be the case in the elderly (Bassey et al. 1998, Kohrt 2001, Suominen 2006). Secondly there is a substantial change in the activity pattern with aging (Westerterp 2000), and the relationship between maximal physical performance and the actual bone loading environment may not be as close in elderly subjects as it is in young subjects. Thirdly, the bone material becomes more brittle with aging and its deformability decreases, which may require lower functional strains in order to retain the yield strain safety factor with increased age (Akkus et al. 2004, Yerramshetty et al. 2006, Yerramshetty & Akkus 2008). Fourthly, a substantial reduction of the bending stiffness of a long bone diaphysis would require bone loss specifically from the periosteal surface, which is highly unlikely. Even after paralysis periosteal bone loss has not been observed (Eser et al. 2004b). Therefore, when loading is decreased (e.g. in aging), the relationship between functional loading and bone rigidity may become non-linear (i.e. increased loading causes linear adaptations in bending strength, whereas decreased loading is not reflected by a linear decrease in bending strength).

10.1.2 Differences between distal tibia and tibial mid-shaft

Altogether the results indicate that the structure of tibial mid-shaft is more strongly dependent on the muscles moving the tibia than the structure of distal tibia. It has been suggested that one of the functions of the trabecular meshwork is to work as a shock absorber underneath joints whereas the purpose of the shaft of the bone is to provide stiff levers for locomotory actions (Currey 2002). The present results seem to support the aforementioned suggestion. Highest compressive loadings on distal part of lower limb in daily activities are likely caused by impacts, which are not necessarily closely related to muscular force production (Komi et al. 1992). In contrast, bending loads on legs are most likely caused by the muscles moving the bone during normal daily activities (Van Buskirk 1989). In addition, distal tibia has functional task in forming the ankle joint. Adult joints and epiphyseal regions are not likely to grow substantially in size, which may explain the lower bone-muscle dependency in the distal tibia observed in the present study (Frost 1997b).

10.2 Body mass and neuromuscular performance as indicators of skeletal loading

Body size (height and weight) and muscle mass have been used as indicators of skeletal loading. Especially muscle mass has been used interchangeably with neuromuscular performance (Blain et al. 2001, Capozza et al. 2004, Henderson et al. 1995, Pettersson et al. 1999, Rector et al. 2009, Taaffe et al. 2001, Witzke & Snow 1999). In the present thesis, the associations between body mass, neuromuscular performance and skeletal rigidity were studied in order to clarify if body mass or muscle volume may be used interchangeably with neuromuscular performance in estimating the skeletal loading environment. The results of these studies indicated that body mass and muscle mass are poorer indicators of skeletal loading environment than neuromuscular performance, highlighting the role of muscles in loading the bones. Increases in the order of 10% in predicting skeletal rigidity were observed on top of the variation explained by body mass and/or muscle volume regardless of age group and gender.

It has conventionally been assumed that body mass is a primary determinant of skeletal rigidity, since a heavier body would impose proportionally higher forces on the bones in a given movement (Heaney & Matkovic 1995). However, Beck et al. (2009) recently reported that femoral neck rigidity scales in proportion to lean mass (Beck et al. 2009). In other words, increased body mass is not related to skeletal loading in a linear fashion. In line with this hypothesis, the results from pre- and postmenopausal women showed an increase of approximately 10% in the total predictive power of the regression model of skeletal rigidity by including performance in addition to height, age and body mass as predictors. Moreover, body mass lost all of its explanatory power when the concentric net impulse was included into the models. Therefore, the present results, as well as several other studies (Lapauw et al. 2009, Macdonald et al. 2006, Nikander et al. 2006, Taaffe et al. 1995), clearly indicate that body mass is poorer indicator of skeletal loading than neuromuscular performance.

10.3 Factors contributing to muscular force production

Muscular force production is determined by muscle volume, specific tension and activation level (Fukunaga et al. 2001). Specific tension can vary between individuals depending on muscle architecture (Fukunaga et al. 2001), muscle fiber distribution (Fitts et al. 1991) and activation level (Narici et al. 2004). The results from young adults indicated that activation level played no role in explaining the bone strength. There seemed to be some variation in activation level among individuals, but evidently activation level is not a major determinative factor in force production in young adults (Merton 1954, Oskouei et al. 2003, Stackhouse et al. 2000). As has been shown previously, the results of the present thesis also suggest that, in addition to variation in muscle volume, there is significant inter-individual variation in specific tension (Ikai & Fukunaga 1968, Maughan & Nimmo 1984), which also plays a role in determining the neuromusucular performance.

10.4 Relationship between ground reaction forces and tibial bone strains

The tibial bone strain modeling conducted in walking confirmed the disagreement between ground reaction forces and bone strains presented by the literature, i.e. the patterns of ground reaction forces, joint moments and tibial bone strains do not coincide (Komi et al. 1992, Lanyon et al. 1975, Silder et al. 2008) (FIGURE 6). Qualitatively it may be speculated that for long bones ground reaction forces should be related to bone strains during concentric phases of force production. The speculation is based on considering that bending forces in the order of 1/50th of compressive forces cause identical maximal strains. Ground reaction forces during eccentric phase of a dynamic activity may reach much higher values than ground reaction forces during the concentric phase (Perttunen et al. 2000). However, a large part of the eccentric phase forces may be caused by the supporting plane decelerating the momentum of body segments and thus the force may be aligned with the long axis of bone causing compressive loading (e.g. heel strike in walking). On the other hand, even though in the concentric phase the ground reaction forces are essentially used to change the momentum of the body segments, the forces are caused by muscles and by the virtue of having moment arms, will always cause bending forces in addition to compressive forces.

10.5 Osteogenic index

It has been suggested that osteogenic index may be valuable in estimating the osteogenicity of a single repetition, exercise session or even the whole exercise regime by including more complexity to the calculation of the index (Turner 1998, Turner & Robling 2003). Recently, Von Stengel et al. (2005,2007) showed that the principles of the osteogenic index, which have been formulated using bone strains from animal models (Turner 1998), are applicable to humans by estimating strains from contact forces (von Stengel et al. 2005, von Stengel et al. 2007). In agreement, the results from comparing the habitual elderly volleyball players to matched controls indicate that osteogenic index may also be applicable to the indirect estimation of bone loading environment by measurement of maximal dynamic performance.

10.6 Implications

Keeping in mind that body mass lost all of its explanatory power in predicting bone strength indices when neuromuscular performance was included into the regression models; let us speculate what would happen, if bone strength could be improved by increasing either body mass or neuromuscular performance. When extrapolating the regression results from the postmenopausal women from regression model 1 (neuromuscular performance not included), it appears that an increase of 1% in body mass is associated with a 0.5% increase in skeletal rigidity. From regression model 2 (neuromuscular performance included and thus no explanatory power for body mass) it appears that a similar increase in performance i.e., impulse, is associated with a 0.5% increase in skeletal rigidity. Therefore, in order to obtain an improvement of five percent in skeletal rigidity, an increase of 10% would be required in either body mass or performance. It is actually known that increase in body mass is not associated with improved skeletal rigidity (van der Voort et al. 2001), whereas improvements in neuromuscular performance have been observed in association with improved skeletal rigidity in exercise interventions (Vainionpää et al. 2007). If we then consider the effects of such an increase in body mass in the postmenopausal group in this study, body mass index would increase from overweight 27 to obese 30, which is clearly an undesirable side effect. Obesity increases mortality (Flegal et al. 2005) and the risk of osteoarthritis in the knee (Niu et al. 2009). On the other hand, improvements of about 10% in physical performance are realistically attainable with exercise, with few counterproductive side effects (Karinkanta et al. 2007, Korpelainen et al. 2006, Uusi-Rasi et al. 2003, Vainionpää et al. 2007). Furthermore, positive effects on cardiovascular risk factors may ensue (Babraj et al. 2009, Heinonen et al. 1996, Vainionpää et al. 2007).

In general, substantial changes in body mass, irrespective of their direction, are associated with osteoporosis (van der Voort et al. 2001). Although weight reduction has been reported to be associated with decreased DXA derived bone density (Shapses & Riedt 2006), a similar association has not been observed in skeletal rigidity with pQCT methodology (Uusi-Rasi et al. 2009). In fact, absolute performance appears to remain quite stable with well executed weight reduction (Fogelholm 1994, Shah et al. 2008, Uusi-Rasi et al. 2009, Zachwieja et al. 2001). In combination with unchanged skeletal rigidity (Uusi-Rasi et al. 2009), the aforementioned observations further support the role of neuromuscular performance in dictating the loading to which bones adapt. The reaction forces and subsequent loads imposed on bones appear to be largely attributable to the type of physical activity. The relative loads may be easily multiplied by changing the type of exercise, e.g. from slow walking to brisk walking or running, as well as a variety of jumping exercises (Heinonen et al. 1996, Vainionpää et al. 2006, Weeks & Beck 2008).

It has previously been shown that power production decreases more markedly with aging than maximal isometric force production capacity (Izquierdo et al. 1999). The results from the habitual volleyball players appear to support the observation that power production capacity can be maintained at an above average level with habitual explosive, e.g. volleyball, training (Ojanen et al. 2007) and the maintained power production maintains bone strength above the average age level (Daly & Bass 2006). The results imply that including explosive actions, i.e. power training, in habitual exercise may have an additional benefit over physical activity in general in terms of maintaining bone strength. Furthermore, a large proportion of bone fractures are caused by falling (Stevens & Olson 2000, Wagner et al. 2009). Power production capacity is related to lower likelihood of falling (Chan et al. 2007, Perry et al. 2007, Sieri & Beretta 2004, Skelton et al. 2002) and better functional ability (Foldvari et al. 2000, Runge et al. 2004) and therefore maintaining power production capacity into advanced age may play a dual role in preventing bone fractures.

10.7 Limitations

As is always the case with cross-sectional designs identification of causal relationship is impossible and only hypothetical suggestions may be raised. The relatively small sample sizes in the present studies particularly somewhat limit the credibility of the correlation results.

The parameters used to characterize neuromuscular performance were thought to give a comprehensive measure of neuromuscular function. However, physical activity level was assessed using self reports, which have been shown to be relatively unreliable (Westerterp 2009). The estimation of muscle volume was also indirect, and its precision is relatively poor. Specific tension estimation relied on the indirect muscle volume estimate and was further simplified by assuming a constant pennation angle and a constant moment arm to fiber length ratio. These assumptions may cause the specific tension estimate to be more a measure of torque production relative to body size rather than a measure of force production relative to physiological cross-sectional area of the muscle.

It is well established that bone mineral density or content may not accurately predict trabecular bone strength (Bevill & Keaveny 2009, Liu et al. 2009). In women, there is a marked change in trabecular structure in the form of reduced connectivity and lost trabeculae in aging, while only trabecular thinning is generally seen in men (Khosla et al. 2006, Lochmuller et al. 2008). The compressive strength index used in the present thesis fails to account for changes in trabecular structure in terms of connectivity and the number of trabeculae. Thus, the BSI_d results may not be comparable between pre- and postmenopausal women, whereas they should be comparable between young and elderly men and between young men and young women. However, the methodology used in the present thesis did not allow for the estimation of trabecular structure.

11 PRIMARY FINDINGS AND CONCLUSIONS

Considering the inaccuracies of the estimations made and the nature of indirect measurements conducted, the following conclusions can be drawn:

1) Even though the pattern of ground reaction forces may differ from the pattern of bone strains, it seems reasonable to use ground reaction forces in estimating skeletal loading.
2) Tibial strength is related to maximal neuromuscular performance in young and elderly men and women. The dependency of bone adaptation to neuromuscular performance seems to be moderate, but site, and loading specific. Neuromuscular performance should be measured and preferred over body mass when regression models for predicting skeletal rigidity are developed and evaluated.
3) At the tibial mid-shaft, the difference in the bone to loading ratio between young and elderly individuals is bigger than expected from the delay in bone adaptation alone.
4) Even in the elderly, habitual explosive exercise seems to be beneficial for the bones.

The results of the present thesis highlight the possibilities for non-pharmacological interventions, namely physical exercise, in maintaining skeletal rigidity. Individual determinants of neuromuscular performance, such as specific tension, have contribution in increasing skeletal integrity and can be positively manipulated with exercises, which are also effective in bone strengthening and fall prevention.

TIIVISTELMÄ (FINNISH SUMMARY)

Neuromuskulaarinen suorituskyky luun geometrian ja voiman selittäjänä ikääntymisen yhteydessä

Osteoporoosi, kaatumiset ja niistä seuraavat luun murtumat aiheuttavat kärsimystä ja taloudellista taakkaa. Lääkeinterventiot eivät ole kustannustehokas tapa ehkäistä näitä osteoporoosiin ja ikääntymiseen liittyviä luun murtumia, joten epäfarmakologisia interventioita, kuten liikunta, on syytä harkita. Tämän väitöstyön tavoitteena oli tutkia kehon massan, neuromuskulaarisen suorituskyvyn (impulssi ja teho erilaisissa hypyissä) ja luuston jäykkyyden välisiä yhteyksiä molemmilla sukupuolilla ja nuorilla ja iäkkäillä koehenkilöryhmillä. Tutkimusten tuloksien perusteella vaikuttaa siltä, että sääriluun jäykkyys on yhteydessä maksimaaliseen neuromuskulaariseen suorituskykyyn nuorilla ja iäkkäillä miehillä ja naisilla. Luun jäykkyyden ja neuromuskulaarisen suorituskyvyn yhteys vaikuttaisi olevan kohtuullinen, mutta kohta- ja kuormitusspesifi. Lisäksi neuromuskulaarinen suorituskyky lisää luun jäykkyyttä ennustavien regressiomallien selitysosuutta kehon massan vaikutuksen lisäksi. Ero luun jäykkyyden ja kuormituksen suhteessa nuorten ja iäkkäiden koehenkilöiden välillä on suurempi kuin mitä voisi odottaa luun adaptaatioviiveen perusteella. Tämä havainto viittaa siihen, että luuston kuormitusherkkyys laskee ikääntymisen yhteydessä. Kuitenkin harrastukseen liittyvät räjähtävät harjoitteet vaikuttavat olevan yhteydessä jäykempiin luihin jopa iäkkäillä. Neuromuskulaarisen suorituskyvyn osatekijät, kuten ominaisjäykkyys, voivat vaikutttaa luuston eheyteen ja suorituskyvyn osatekijöitä voidaan manipuloida positiivisesti harjoitteilla, jotka ovat tehokkaita myös kaatumisten ehkäisyssä.

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