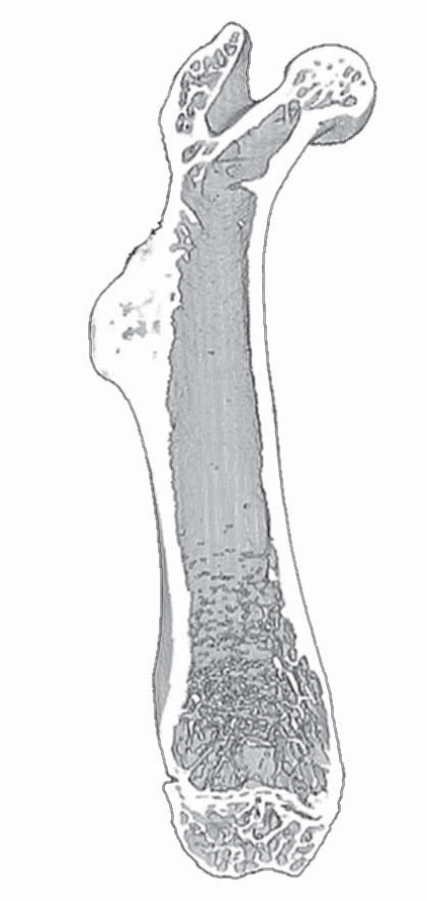
STUDIES IN SPORT, PHYSICAL EDUCATION AND HEALTH
172

Hongqiang Ma

Adaptation of Bone to Physical Activity and Diet-Induced Obesity



JYVÄSKYLÄN YLIOPISTO

STUDIES IN SPORT, PHYSICAL EDUCATION AND HEALTH 172

Hongqiang Ma

Adaptation of Bone to Physical Activity and Diet-Induced Obesity

Esitetään Jyväskylän yliopiston liikunta- ja terveystieteiden tiedekunnan suostumuksella
julkisesti tarkastettavaksi yliopiston vanhassa juhlasalissa S212
syyskuun 10. päivänä 2011 kello 12.

Academic dissertation to be publicly discussed, by permission of
the Faculty of Sport and Health Sciences of the University of Jyväskylä,
in auditorium S212, on September 10, 2011 at 12 o'clock noon.

UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2011

Adaptation of Bone to Physical Activity and Diet-Induced Obesity

STUDIES IN SPORT, PHYSICAL EDUCATION AND HEALTH 172

Hongqiang Ma

Adaptation of Bone to Physical Activity and Diet-Induced Obesity

UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ 2011

Editors
Harri Suominen
Department of Health Sciences, University of Jyväskylä
Pekka Olsbo, Ville Korkiakangas
Publishing Unit, University Library of Jyväskylä

URN:ISBN:978-951-39-4401-8
ISBN 978-951-39-4401-8 (PDF)

ISBN 978-951-39-4400-1 (nid.)
ISSN 0356-1070

Jyväskylä University Printing House, Jyväskylä 2011

ABSTRACT

Hongqiang, Ma
Adaptation of bone to physical activity and diet-induced obesity
Jyväskylä: University of Jyväskylä, 2011, 146 p.
(Studies in Sport, Physical Education and Health
ISSN 0356-1070; 172)
ISBN 978-951-39-4400-1 (nid.)
ISBN 978-951-39-4401-8 (PDF)
Finnish summary
Diss.

Bone, as the main component of the skeleton, is constantly formed and renewed by modeling and remodeling in response to mechanical and non-mechanical factors throughout the lifespan; meanwhile it also actively involves multiple metabolic and structural functions. Two closely related disorders of body composition, osteoporosis and obesity, remain a major public health concern and are growing in prevalence world-wide. Although physical activity, as a non-drug anabolic therapy, has been shown to be an efficient tool in the enhancement of bone and the improvement of obesity-related unhealthy status, the underlying mechanisms remain unclear. Thus, the purpose of the present study was to investigate the association of physical activity, diet-induced obesity, and their combination with bone properties.

In a population-based study, twin pairs discordant for leisure time physical activity for at least 30 years were employed. This study showed that long-term leisure time physical activity was associated with larger cortical bone cross-sectional area, thicker cortex, and greater moment of inertia at the tibial shaft, and with increased trabecular bone mineral density and compressive strength index at the distal tibia. The results in monozygotic co-twins confirmed that physical activity during adulthood was associated with stronger bones.

In an animal study, combined diet-induced obesity and voluntary physical activity was employed in mice during growth. This study showed that both obesity and voluntary physical activity affected bone properties, and that body mass had more pronounced effects on bone than voluntary wheel running. Diet-induced obesity was associated with elevated bone size and mass as well as strength surrogates such as moments of inertia and compressive strength-strain index, but not with tissue mineral density measured by pQCT in the diaphysis and distal metaphysis of the femur. Enlarged bone size and increased mineral content of cortical and trabecular bones in obese mice were also observed. However, the obese mice had increased bone mineral density measured by pQCT in the cortical bone in the diaphysis, but not in the trabecular bone in the metaphysis. On the other hand, in microCT measurements, the obese mice had increased bone mineral density in the trabecular compartment of the metaphysis but not in the cortical bone. Increased trabecular thickness in obese mice was observed both at the femoral metaphysis and the vertebral body. Voluntary wheel running was associated with decreased tissue bone mineral density and compressive stress index in the femoral metaphysis, and thinner cortical thickness in the diaphysis, especially in lean mice. However, in obese mice runnning was also associated with smaller marrow cavity and increased plate-like trabeculae in the distal metaphysis.

These results suggest that in mice bone adapts to body weight and physical activity by optimizing bone strength on both the whole bone and microstructure levels in a site-specific manner.
Keywords: physical activity, bone, obesity, microstructure, mineral density

Author's address

Hongqiang Ma
Department of Health Sciences
P.O Box 35 (LL)
FI-40014 University of Jyväskylä, Finland

Supervisors

Professor Harri Suominen
Department of Health Sciences
University of Jyväskylä

Professor Urho Kujala
Department of Health Sciences
University of Jyväskylä

Professor Heikki Kainulainen
Department of Biology of Physical Activity
University of Jyväskylä

Reviewers

Docent Teppo Järvinen
Helsinki University Hospital

Docent Petteri Nieminen
School of Medicine
Institute of Biomedicine/Anatomy
Faculty of Sciences
University of Eastern Finland

Opponent

Professor Kalervo Väänänen
University of Eastern Finland

ACKNOWLEDGEMENTS

This study was conducted at the Department of Health Sciences in collaboration with the Department of Biology of Physical Activity and the Department of Physics in the University of Jyväskylä during 2008-2011.

I express my sincere thanks to my supervisors Professor Harri Suominen, Professor Urho Kujala, and Professor Heikki Kainulainen. You have created a congenial atmosphere in our collaborative research group. Thank you for trusting me and giving me this opportunity and the freedom to follow my own ideas. The criticism and support received during the preparation of the manuscript of this thesis are greatly appreciated.

I owe my deepest gratitude to my tutor and dear friend, Paavo Rahkila. You have taught me a great deal about research and science. Thank you for always finding time for me and for discussing work, life, and study, and for all your guidance and expert advice in the lab and office during everyday life.

I thank the official examiners of this thesis, Docent Teppo Järvinen and Docent Petteri Nieminen, for their constructive criticism and valuable comments.

I thank Professor Jussi Timonen for providing me with the facilities to scan my bone samples and Professor Juha Tuukkanen for providing me the possibility for bone histomorphometry.

I would like to thank my co-authors Tuomas Turpeinen, Mika Silvennoinen, Sira Torvinen, Tuija Leskinen, Rita Rinnankoski-Tuikka, Markku Alen, Sulin Cheng, Sarianna Sipilä, Ari Heinonen, Jaakko Kaprio, Zhiqi Peng, and Jukka Morko. For help and advice given in the laboratory work and in preparing the samples, I am grateful to Mika and Sira; to you I also owe special thanks for being good friends and excellent colleagues during these years. I am deeply grateful to Tuomas Turpeinen for his assistance with the image processing. Without you, it would have been impossible to finish the image analysis!

I also want to thank the excellent personnel at our biochemistry laboratory. Kaisa-Leena Tulla, Erkki Helkala, and Tuovi Nykänen are acknowledged for their skilful assistance. The secretary at the Department of Health Sciences, Marja Petman, is thanked for her invaluable help in all the paper work and bureaucracy.

I am grateful for the financial support I have received for carrying out this study. This work was supported via project funding from the Academy of Finland, from the National Doctoral Programme of Musculoskeletal Disorders and Biomaterials, and from the Rector grant of University of Jyvaskyla. Michael Freeman is acknowledged for revision of the English language of the original papers and the thesis book.

My deepest love and gratitude go to my family. I warmly thank my parents and parents-in law who taught and encouraged me not to give up when the first difficulty occurs and to complete the tasks once started. Finally, I would like to express my deepest gratitude to my dear wife Yaqiong Cui for her

understanding and support, especially during times of difficulty with my study. Special thanks go to my mother-in-law. You have done a lot for our family especially since last winter when our daughter Manyi Ma came into the world.

Jyväskylä 28.7.2011
Hongqiang MA

LIST OF ORIGINAL PUBLICATIONS

The thesis is based on following original articles, which are referred to in the text by their Roman numerals. In addition, some unpublished data are presented in the thesis.

I. Ma H, Leskinen T, Alen M, Cheng S, Sipilä S, Heinonen A, Kaprio J, Suominen H, Kujala UM. Long-term leisure time physical activity and properties of bone: a twin study. J Bone Miner Res. 2009; 24:1427-33.

II. Ma H, Torvinen S, Silvennoinen M, Rinnankoski-Tuikka R, Kainulainen H, Morko J, Peng Z, Kujala UM, Rahkila P, Suominen H. Effects of diet-induced obesity and voluntary wheel running on bone properties in young male C57BL/6J mice. Calcif Tissue Int. 2010; 86:411-9.

III. Ma H, Turpeinen T, Silvennoinen M, Torvinen S, Rinnankoski-Tuikka R, Kainulainen H, Timonen J, Kujala UM, Rahkila P, Suominen H. Effects of diet-induced obesity and voluntary wheel running on the microstructure of the murine distal femur. Nutr Metab (Lond). 2011; 8:1.

IV. Ma H, Silvennoinen M, Turpeinen T, Torvinen S, Rinnankoski-Tuikka R, Kainulainen H, Timonen J, Kujala UM, Rahkila P, Suominen H. Cortical porosity, trabecular microstructure, and density distribution in the distal femur of obese mice. (Submitted for publication)

ABBREVIATIONS

aBMD	Areal bone mineral density
AFM	Atomic force microscopy
AGEs	Advanced Glycation End products
BA	Bone area measured from DXA
BMC	Bone mineral content from DXA
BMC_{tot}	total cross-sectional BMC
BMD	Bone mineral density
BMPs	Bone morphogenetic proteins
BMU	Basic multicellular unit
BRC	Bone-remodeling compartment
BS	Trabecular bone surface
BSI	Bone strength index
BUA	Broadband attenuation
BV	Trabecular bone volume
BV/TV	Trabecular bone volume to total bone volume ratio
C	Control diet
Conn.D	Connectivity density
CR	Control diet +voluntary wheel running
CSA_{bone}	Bone cross-sectional area without marrow
CSA_{co}	Cortical bone cross-sectional area
CSA_{m}	Marrow cross-sectional area
CSA_{tot}	Total tibia cross-sectional area
CSI	Compressive stress index
CSMI	Cross-sectional moment of inertia
CT	Computed tomography
DXA	Dual x-ray absorptiometry
FEA	Finite element analysis
FTIR	Fourier transform infrared imaging micro-spectroscopy
HSA	Hip structure analysis
HF	High-fat diet
HFR	High-fat diet + voluntary wheel running
Hr-pQCT	High-resolution peripheral computed tomography
Hr-MRI	High-resolution magnetic resonance imaging
HRT	Hormone replacement therapy
IGF-1	Insulin growth factor-1
Imax	Maximum moment of inertia
Imin	Minimum moment of inertia

Ipolar	Polar moment of inertia
LTPA	Leisure time physical activity
M-CSF	Macrophage-colony stimulating factor
MRI	Magnetic resonance imaging
μCT	Micro-computed tomography
μMRI	Micro-magnetic resonance imaging
NCPs	Non-collagenous proteins
NO	Nitrogen oxide
OI	Osteogenesis imperfect
OPG	Osteoprotegerin
PMMA	Poly-methylmethacrylate
pQCT	Peripheral quantitative computed tomography
PTH	Parathyroid hormone
QCT	Quantitative computed tomography
QUS	Quantitative ultrasound
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
SMI	Structure model index
SOS	Speed of the sound
SSI	Stress-strain index
Tb.N	Trabecular number
Tb.Pf	Trabecular pattern factor
Tb.Sp	Trabecular separation
Tb.Th	Trabecular thickness
TGF-β	Transforming growth factor-beta
Th_c	Cortical thickness
$vBMD_{bone}$	volumetric bone mineral density
$vBMD_{co}$	volumetric cortical bone mineral density
$vBMD_{tot}$	volumetric tibia mineral density
$vBMD_{trab}$	volumetric trabecular bone mineral density
VEGF	Vascular endothelial growth factor
vQCT	Volumetric quantitative computed tomography
XRD	X-ray diffraction

CONTENTS

1 INTRODUCTION

Bone tissue during the lifetime has the capacity to modify itself in response to mechanical and/or non-mechanical factors; it also serves as an endocrinal organ coordinating with other systems. Mechanical loading exerted either by dynamic actions, such as physical activity, and static loads, such as body mass or their combination, has long been observed to affect bone properties. However, whether the association between these two types of mechanical load and bone is negative or positive remains unclear, especially as with respect to the adaptation to mechanical loading of cortical and trabecular compartments. Currently, peripheral quantitative computed tomography (pQCT) for the evaluation of trabecular and cortical bone and high-resolution micro-computed tomography (μCT) for 3-D structure measurements have been adopted in the bone research field. These led to the present interest in studying the effects of mechanical loading caused by physical activity and body weight on cortical and trabecular bone as well as on their 3D microstructure.

Numerous studies have documented that leisure time physical activity associates with improved bone properties (Daly and Bass 2006; Hamilton et al. 2010; Morseth et al. 2010). However, most of this evidence is derived from observational follow-up studies or short-term randomized controlled trials (RCTs). It is known that genetic factors are important in bone development, but mechanical loading, i.e., physical activity, affects the final form (Rauch and Schoenau 2001; Ferretti et al. 2003). Observational studies of the association between physical activity and bone properties in unrelated individuals may include a bias due to genetic factors, and in addition there are no proper long-term RCTs. Thus, there is little replicated and methodologically sound information to show the potential of long-term physical activity during adulthood or old age in improving bone health. In the present study, a unique design with twin pairs discordant for long-term leisure time physical activity (LTPA) over 30 years was used to investigate the association between LTPA and bone properties and to elucidate how trabecular and cortical bone respond to LTPA.

Recently, a close link between body mass and bone mass has been established (Reid 2008; Iwaniec et al. 2009). An association between low body mass and increased risk of osteoporotic fractures due to low bone mass has also been reported (Galusca et al. 2008). Decreased mechanical loading resulted in bone loss has been well documented both in human subjects under the conditions of bed rest (Holguin et al. 2009) and spaceflight (Goodship et al. 1998) and in unloaded animals (Bikle and Halloran 1999; Vajda et al. 2001). At the other extreme, increased body mass in obese subjects has been shown positively to associate with bone mass and strength (Cobayashi et al. 2005; Aubertin-Leheudre et al. 2008), while other studies have reported a negative association (Braillon and Serban 2007; Goseki-Sone et al. 2007). The mechanism by which body mass affects bone properties either by direct mechanical loading or by indirect biological reactions remains largely undetermined. In the present studies, conducted with mice, the effects of diet-induced obesity on the trabecular and cortical bone compartments as well as bone marrow adiposity, and how diet-induced obesity during growth affects bone properties were addressed.

Further, in the animal studies, voluntary wheel running was used to investigate how exercise, diet-induced obesity, and their combination affect bone properties. Although forced exercises on a treadmill or jumping have been shown the positive effect of physical activity on bone strength (Umemura et al. 2002; Wu et al. 2004; Hamrick et al. 2006), forced-exercise models may be problematic due to stress, and thus voluntary wheel running offers a better model. A few studies have indicated that voluntary exercise can improve bone properties through bone modelling or remodelling (Mori et al. 2003; Wu et al. 2004; Banu et al. 2006; Plochocki et al. 2008). Therefore, the overall purpose of this study was to determine how bone adapts to diet-induced obesity and physical activity.

2 REVIEW OF THE LITERATURE

2.1 Overview of the skeleton and bone

The skeletal system, which is of vital importance to the body both biomechanically and metabolically, is comprised of individual bones and connective tissues (cartilage, ligaments, and joints of the body). Bone constitutes the majority of the system and is a specialized form of mineralized connective tissue which differs from other connective tissues in rigidity and hardness. The rigidity and hardness of bone enables the skeleton to serve structural functions, including maintenance of body shape, protection of the internal organs/soft tissues of the cranial, thoracic, and pelvic cavities, housing for bone marrow, and points of attachment for skeletal muscles as well as transition of the force of muscular contraction from one part of the body to another during movement. The skeleton has an essential metabolic function, playing a central role in mineral homeostasis, principally of calcium and phosphate ions, but also of sodium and magnesium (Kartsogiannis and Ng 2004). Most recently, the evidence from animals with genetic manipulation of cytokines and their receptors have shown that the skeleton also behaves as an endocrine organ secreting factors to regulate energy metabolism (Lee et al. 2007; Rosen 2008; Confavreux et al. 2009; Fukumoto and Martin 2009).

Although the skeleton's principal role as a structure has led bone to have the unfortunate reputation of being an inert and static material, bone tissue is a 'smart' and 'dynamic' material that undergoes significant turnover in the same way as the other organs in the body. It is able to accommodate, adjust, and adapt its mass, shape, and properties to changes in mechanical or metabolic requirements and endures voluntary physical activity for the purpose of everyday life without fracture or pain.

2.2 Basic components of bone as a tissue

Bone tissue is an ensemble of bone cells and their extracellular matrices as well as blood vessels and nerves. By weight, approximately 60% of the tissue is inorganic matter, 8-10% is water, and the remainder is organic matter. By volume, these proportions are approximately 40%, 25%, and 35%, respectively. The inorganic phase is an impure form of hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$), which is a naturally occurring calcium phosphate (Mkukuma et al. 2004). The organic phase is composed predominantly (over 90% by weight) of type I collagen and a variety of noncollagenous proteins, and cells make up the remaining 2% of this phase (Marcus et al. 2009).

2.2.1 Bone cells

Four different types of cells can be identified: osteoblasts, lining cells, osteocytes, and osteoclasts.

Osteoblasts, located on the surface of the mineralized matrix, are mononuclear cells originated from bone marrow mesenchymal stem cells and responsible for the formation of new bone by synthesizing and regulating the deposition and mineralization of the extracellular matrix (Mackie 2003). A large number of paracrinal, autocrinal, and endocrinal factors affect osteoblast development and maturation, such as bone morphogenetic proteins (BMPs), growth factors (e.g., insulin growth factor, IGF), and fibroblast growth factors (e.g., vascular endothelial growth factor). Osteoblasts also secret regulators of matrix mineralization such as osteocalcin, osteopontin, receptor activator of nuclear factor kappa-B ligand (RANKL) and osteoprotegerin (OPG) which also regulate osteoclast differentiation and activity. Osteoblasts contain a prominent Golgi apparatus and a well-developed rough endoplasmic reticulum. After ceasing matrix-forming activity, osteoblasts can undergo apoptosis, terminal differentiation into osteocytes, or remain in inactive form as so called *lining cells* on the bone surface (Dallas and Bonewald 2010). In addition, osteoblasts adjacent to bone marrow provide the microenvironment, or niches, for hematopoietic stem cells and vice versa, which give rise to cells of the myeloid lineage, including osteoclasts (Mackie 2003; Wu et al. 2009).

Osteocytes are non-proliferative, terminally differentiated cells of the osteoblastic lineage. As the most abundant cells in bone, they reside both in the mineralized bone matrix and in newly formed osteoids in both woven and lamellar bone (Franz-Odendaal et al. 2006; Noble 2008). The formation of osteocytes has been considered a passive process in which some osteoblasts are trapped or "buried" in osteoid, recent studies also suggest this process may actually be an active rather than passive process (Dallas and Bonewald 2010). Osteocytes are located in the lacuna-canalicular system and connect to neighboring cells through cytoplasmic protrusions. This network permits direct communications between neighboring osteocytes, lining cells and osteoblasts

on the bone surface as well as blood vessels (Lane and Yao 2009). Since ostecytes form a network spanning the whole individual skeletal bone, they may well, through their residual metabolic activity, play a role in bone turnover. Osteocytes have numerous functions, such as involvement in bone remodeling through regulation of both osteoclast and osteoblast activity and functioning as an endocrine cell to interact with other organs, such as kidney, muscle, and other tissues (Bonewald 2006; Bonewald 2007; Bonewald 2010; Dallas and Bonewald 2010). Osteocytes can detect changes in the levels of hormones, such as estrogen and glucocorticoids as well as the parathyroid hormone, that influence their survival rates. Osteocytes probably act as mechanosensors that signal the need for bone modeling to adapt the bone to functional loading according to Wolff's law (Frost, 2004) and remodeling to repair micro-structural changes within the bone matrix or both.

Osteoclasts are located on the bone surfaces within Howship's lacunae, also known as resorption lacunae and considered to be the exclusive bone-resorbing cells. They are large multinucleated cells derived from the fusion of mononuclear hematopoietic precursors and contain large numbers of lysosomes, and mitochondria, and have an extensive Golgi complex. Their differentiation is dependent on the presence of two critical factors—a secreted cytokine, macrophage-colony stimulating factor (M-CSF) and a cell-surface protein, receptor activator of nuclear factor kappa-B ligand (RANKL) derived from hematopoietic stem cells—which bind to their corresponding receptors on osteoclast progenitors (Väänänen and Laitala-Leinonen 2008; Yavropoulou and Yovos 2008). Active osteoclasts are rarely found in normal bone, but at sites of high bone turnover, such as in the metaphysis of growing bone or in the trabecular bone of osteoporosis, where they appear in increased numbers. Generally, all osteoclasts are considered to be alike, independent of the skeletal site; however, recent data suggest bone-site-specific osteoclast heterogeneity exists (Everts et al. 2009).

2.2.2 Extracellular matrix

Organic phase

The organic bone matrix contains approximately 90% of type I collagen, along with a small quantity of types III, V and X collagen (Parfitt 1983); the remaining about 10% consists of non-collagenou components. In general, the 'backbone' of bone matrix is composed of parallel aligned collagen fibers, interspersed with bundled collagen fibrils, formed by cross-linked pro-collagen which is a helical rod of three intertwining polypeptide chains (two identical α1 helices and one different α2 helix) (Figure 1). Parallel aligned collagen fibers are arranged in a quarter-staggered end-overlap fashion, forming numerous gap regions, where hydroxyapatite crystals are located along with the mineralization process. Trace amounts of type III, V and X collagen may regulate the diameter of collagen fibrils during certain stages of bone matrix formation (Rho et al. 1998).

Non-collagenous proteins play an important role in the regulation of the formation and growth of hydroxyapatite crystals in the specific sites of the

collagen fibers and control a variety of cell activities (Sodek et al. 2002). Among them, the most abundant are osteocalcin, osteonectin (Delany et al. 2003), osteopontin (Sodek et al. 2002; Thurner et al. 2010) and bone sialoprotein (Ganss et al. 1999). Osteocalcin has been found to not only participate in the regulation of mineralization and calcium ion homeostasis and of activities of osteoclasts and osteoclast precursors, but is also involved in energy metabolism through regulating insulin levels (Lee et al. 2007; Confavreux 2011). Bone sialoprotein enhances osteoblast differentiation and matrix mineralization *in vitro* (Gordon et al. 2007), but decreases osteoblast population and increases osteoclast activity when over-expressed *in vivo* (Valverde et al. 2008). Other noncollagenous proteins are also involved in the regulation of bone homeostasis. Various products from the breakdown of bone matrix in blood and urine samples have been used as biomarkers reflecting bone turnover levels (Robins 2003; Seibel 2005).

Bone matrix also contains very small quantities of growth factors and cytokines like IGF, OPG, the interleukin, BMPs, and transforming growth factor-beta (TGF-B) (Noda and Rodan 1989). These proteins have important effects on bone cell differentiation, activation, growth, and turnover and also likely serve as coupling factors during remodeling. A layer of round lipid particles beneath the minerals has also been identified and is thought to mediate collagen calcification in compact bone formation (Xu and Yu 2006).

Inorganic phase

The majority of bone mineral is hydroxyapatite, which exists in the form of needle-, plate- or rod-shaped crystals, residing in the gap regions of collagen fibers. Bone mineral also contains many impurities such as carbonate, citrate, magnesium, fluoride and strontium, which incorporate either into the crystal lattice or the collagen fibril, facilitating the solubilization of bone in order to serve as a mineral ion bank to meet the homeostatic demands of the whole body. As mineralization occurs, a variety of bone seeking agents, like tetracycline and radio-nuclides (Stepensky et al. 2003), can also be incorporated into the bone matrix, providing the possibility to investigate dynamic bone activity. The inorganic phase ultimately contributes to bone mechanical rigidity and load bearing capacity, but as the degree of mineralization increases, bone may be too brittle or fragile, reducing the energy required to fracture (Turner 2002).

Water

Water accounts for 25% of the volume of bone and is distributed throughout the tissue in various forms either freely mobile in the vascular-lacunar-canalicular space or bound to the collagen network and the mineral phase (Nyman et al. 2005). Water plays an important role in the initialization of bone mineralization and stabilization of defect-containing crystals as well in mediating mineral-organic matrix interactions (Wilson et al. 2006), and it further influences bone mechanical properties (Utku et al. 2008). Changes in bone water content are also associated with bone pathological status (Techawiboonwong et al. 2008).

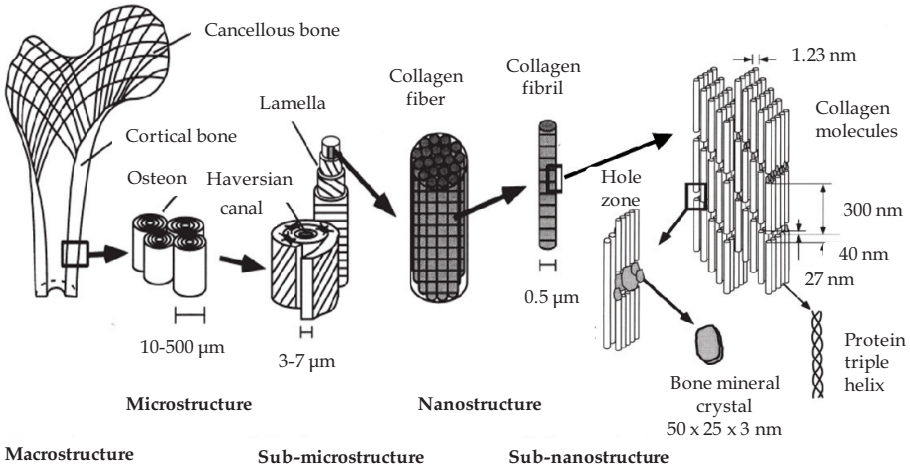


FIGURE 1 Bone hierarchical organization from the macro- to micro- to nano-level. Modified from Rho et al. (1998).

2.3 Bone structure

2.3.1 Macrostructure

Two distinct forms of bone can be distinguished in the long bone: cortical and trabecular bone. Cortical or compact bone, which forms the outer shell of bone, is thin in the epiphyseal and metaphyseal regions, but is thick in the diaphyseal region. Trabecular, cancellous, or spongy bone, which occupies the inner region of the bone, is located in the epiphysis and metaphysis in long bones, and makes up the greater part of vertebral bodies. However, the proportion of each tissue type varies greatly between different bone sites.

Cortical bone accounts for most of the entire adult skeletal mass in humans but has a lower surface-volume ratio, indicating a low turnover rate. It supplies biomechanical, supportive, and protective functions. Cortical bone matrix is not solid material, but has a complex canal network formed by interconnected Haversian canals and Volkmann's canals. Haversian canals run nearly parallel with the major axis of bone, while Volkmann's canals are oriented perpendicular to the skeleton loading axis and run horizontally from the periosteal surface to the endocortical surface of the cortical bone. Circulatory vessels and nerves as well as an extracellular fluid run through this three dimensional network of canals allowing exchange of nutrition, nerve signals, and metabolites between bone and its neighboring environment.

In contrast, trabecular bone accounts for a small fraction of the total bone mass. Trabecular bone is composed of a large number of inter-connected rod- or plate- like trabeculae, which form a sponge-like trabecular network. Compared to cortical bone, it has a larger surface-volume ratio, resulting in a high turnover rate. The main function of the cancellous bone is to provide biomechanical flexibility and fulfill homeostatic demands.

2.3.2 Microstructure

Under a microscope, based on matrix organization, two types of bone can be identified: woven and lamellar bone.

Woven bone is immature bone which is rapidly formed and randomly arranged during embryonic skeletal development, longitudinal bone growth under the growth plate, and early fracture healing, and is eventually resorbed and replaced by lamellar bone. Due to its randomly orientated and loosely bundled collagen fibers and low mineral deposition, the mechanical strength of woven bone is weak.

In contrast, lamellar bone is mature bone which is formed at a much slower rate and is strictly organized during bone formation on the existing bone surfaces. Collagen fibers in the same layer within lamellar bone are laid parallel to each other forming a bone matrix sheet, or lamella structure but in the next layer perpendicular to that of the previous layer. As such, on a bone histological section, the transverse and longitudinal-oriented collagen fibers display an alternative dark-light pattern under polarized light (Boyde and Riggs 1990; Bromage et al. 2003). In adult cortical bone, three distinct lamellar patterns can be recognized: 1) a Haversian system or osteon which is formed by concentric layers of lamellar sheets surrounding a longitudinally vascular channel (Congiu and Pazzaglia 2011); 2) circumferential lamellae formed by multiple layers of lamellar sheets continuously around part or all of either the periosteal or endosteal surfaces; and 3) interstitial lamellae which are fragments of old lamellae located in between osteons. Similarly, trabecular bone contains two major lamellar patterns: 1) trabecular packets, which are hemi-osteon-shaped shallow crescents (Boel et al. 2007) and 2) interstitial lamellae (Jee 2001). The mechanical strength of lamellar bone is strong due to its orderly orientated and stably bundled collagen fibers and high degree of mineralization.

2.3.3 Bone functional unit

The structural units of bone are the osteon in cortical bone and the hemi-osteon in trabecular bone, and are the end products of bone remodeling. These structural units provide the frameworks for different cell types working together in a highly synchronized fashion in response to mechanical and non-mechanical factors. Basic multicellular unit (BMU) is a functional term defining a unit comprising cells (progenitors, lining cells, osteoclasts, osteoblasts, osteocytes, and other cells) involved in the remodeling process (Frost 1964).

2.4 Bone modeling and remodeling

2.4.1 Modeling

Bone modeling is responsible for growth and mechanically induced adaptation of bone that governs the enlargement of each individual bone during growth and when needed. During modeling, bone formation and resorption are not tightly coupled (Raggatt and Partridge 2010). Modeling by formation without being coupled to resorption increases bone size on the periosteal surface and formalizes bone shape according to a genetic "blueprint" and as an adaptive response to prevailing loads (Murray and Huxley 1925). Resorption without subsequent formation occurs on the endocortical, intracortical, and trabecular surfaces, excavating a marrow cavity during growth and establishing cortical and trabecular architecture (Hattner et al. 1965). It also occurs on the periosteal surface during growth, particularly at the metaphyses, fashioning the cone-like ends of long bones (Rauch and Schoenau 2001; Rauch et al. 2001). Therefore, modeling is involved not only in the development of normal architecture during growth, but also in the modification of this architecture and mass in response to alterations in mechanical conditions. After skeletal maturity, during aging, bone deposition on the periosteal surface partially compensates for the loss of bone strength caused by endocortical resorption (Smith and walker 1964; Ruff and Hayes 1982; Ahlborg et al. 2003; Seeman 2003). Bone modeling may also be increased in patients suffering from bone related-diseases (Clarke 2008).

2.4.2 Remodeling

Bone remodeling is responsible for repairs of aged bone tissue that is damaged or mechanically unfits to maintain the integrity of the skeleton and mineral homeostasis in response to mechanical and non-mechanical stimuli throughout the lifespan (Raggatt and Partridge 2010). Remodeling begins before birth and lasts until death (Clarke 2008), involving the replacement of immature woven bone with the more biomechanically and metabolically competent lamellar bone, conversion of the primary spongiosa woven bone into the secondary spongiosa lamellar bone during growth, and repair of unfit or damaged bones during adulthood. Due to the much larger surface-to-volume ratio, trabecular bone is more actively remodeled than cortical bone. During remodeling, resorption and formation are tightly coordinated and regulated by central, systemic and local factors. With aging, the coupling between bone formation and resorption becomes imbalanced, as in osteoporotic bone, a focal bone deficit or a negative bone balance being created in each remodeling cycle (Downey and Siegel 2006). The overall deficit leads to age-related bone loss.

Bone remodeling is performed by clusters of bone-resorbing osteoclasts and bone-forming osteoblasts together with other assistant cells and regulating factors arranged in temporary anatomical structures known as BMUs (Figure 2). A canopy of cells, called "osteomacs" (Chang et al. 2008; Pettit et al. 2008;

Winkler et al. 2010), together with adjacent capillaries, form a bone-remodeling compartment (BRC) which traverses and encases the BMUs and provides the microenvironment for efficient bone remodeling (Hauge et al. 2001; Parfitt 2001; Andersen et al. 2009; Eriksen 2010). In response to the different stimuli, two types of remodeling exist: 1) targeted remodeling activated by and repairing fatigue microdamage, and 2) non-targeted remodeling serving purposes such as calcium homeostasis (Burr 2002; Parfitt 2002a). Bone remodeling is affected by a variety of factors, e.g., local structural, metabolic, mechanical and non-mechanical, but the underlying mechanisms remain unclear. The bone remodeling cycle includes 5 sequential phases (Tran Van et al. 1982a): activation, resorption, the reversal phase, formation, and quiescence (Figure 2).

Activation involves the recruitment and activation of hematopoietic mononuclear osteoclast precursors at the sites of resorption, detachment of the endosteum, fusion of precursors, and attachments of multinucleated osteoclasts to the bone surface (Clarke 2008; Sims and Gooi 2008). The osteoblastic lineage cells play a critical role in each step of this process; however, the exact cell population of this lineage has not been fully determined. Osteocytes, as mechano-sensors detecting mechanically unfit and damaged matrix, or increased demand for mineral ions, produce an activation signal to initiate the bone remodeling process. This signal induces the ingrowth of capillaries and stimulates the bone-lining cells to contract themselves and to release factors that digest the underlying osteoid layer to expose the mineralized surface. Detached bone-lining cells may migrate into the adjacent marrow and directly communicate with osteoclastic precursors through cell-cell contact to initiate osteoclastogenesis. On the other hand, loss of osteocytes through apoptosis (Aguirre et al. 2006; Henriksen et al. 2009) or conditional ablation (Tatsumi et al. 2007) also increases osteoclast number. Mature osteoclasts migrate and attach to the exposed mineralized surface, forming ruffled borders, and resorption starts.

Resorption is the phase in which osteoclasts erode the bone, forming cavities referred to as Howship's lacunae in cancellous bone (Figure 2), and as cutting cones in cortical bone (Figure 3).

Reversal (coupling) refers to an interval between the completion of resorption and the commencement of formation where the osteoclasts fade away and the osteoid starts to appear. Arrays of unknown mononuclear cells cover this surface and prepare for bone formation. Some authors suggest that monocytes close to the osteoclasts are capable of digesting and clearing the demineralized matrix while cells close to the osteoid, whic form a reversal cement line, are considered to be preosteoblasts (Tran Van et al. 1982b; Domon et al. 2001).

Sequentially, preosteoblasts aided by "coupling factors" differentiate into mature functional osteoblasts, initiating the *formation phase*. Mature osteoblasts synthesize and secrete type I collagen fibers, forming tropocollagens which later cross-link and form the gap-regions for the deposition of mineral crystals. As osteoid matures, osteocytes regulate an influx of mineral ions from the extracellular fluid to form hydroxyapatite molecule crystals. The process of

mineralization starts at the interface between mineralized bone and unmineralized osteoid, and then advances toward the upper lamellar layer. Upon completion of bone formation, a one-micron layer of unmineralized matrix remains on the bone surface. During this process, most osteoblasts remain on the top; a few lag behind and are entombed in lacunae with their processes extending circumferentially into the canaliculi. These cells differentiate into osteocytes and communicate to their neighboring osteocytes or bone lining cells through gap-junctions establishing a 3D osteocytic lacunae-canaliculi network throughout the entire bone. After bone formation, osteoblasts either differentiate into bone-lining cells or enter apoptosis.

Once an equal quantity of resorbed bone has been replaced, the surface enters into the *resting (quiescent) stage*. The bone surfaces are covered by bone-lining cells and an endosteal membrane, a 0.1 µm layer of unmineralized connective tissue with fewer collagen fibers and less amorphous ground substance than found in bone. A variety of factors regulate each step of bone remodeling, including RANKL, OPG, M-CSF, IL-1 and IL-6, TGF-β, PTH, 1,25-dihydroxyvitamin D and calcitonin, BMP_2, IGF-I and II as well as sclerostin, which is produced by osteocytes and is the key player in the initiation and termination of remodeling (Boyle et al. 2003; Raggatt and Partridge 2010; Tachi et al. 2010). In addition to these growth factors and cytokines, simple molecules like nitric oxide (NO) (Chae et al. 1997; Mancini et al. 1997; Saura et al. 2010) and hypoxia and acidosis (Arnett et al. 2003; Utting et al. 2006; Arnett 2010; Utting et al. 2010) also exert pronounced effects on bone remodeling activity.

2.4.3 Bone turnover

Bone turnover refers to the sequential process of bone remodeling and depends on the surface-restricted activation frequency and on the surface-to-volume ratio. Activation frequency is the intensity of remodeling, the reciprocal of the average time interval between the start of consecutive cycles of remodeling at the same site. In general, biopsies for turnover estimation in the human skeleton are taken from a rib or ilium, used for cortical and trabecular bone respectively. Normally, cortical turnover in the rib is lower than that in the ilium. However, turnover is not always higher in cancellous than in cortical bone (Parfitt 2002b). In response to different physiological or pathological conditions, the turnover rate varies at different skeletal sites.

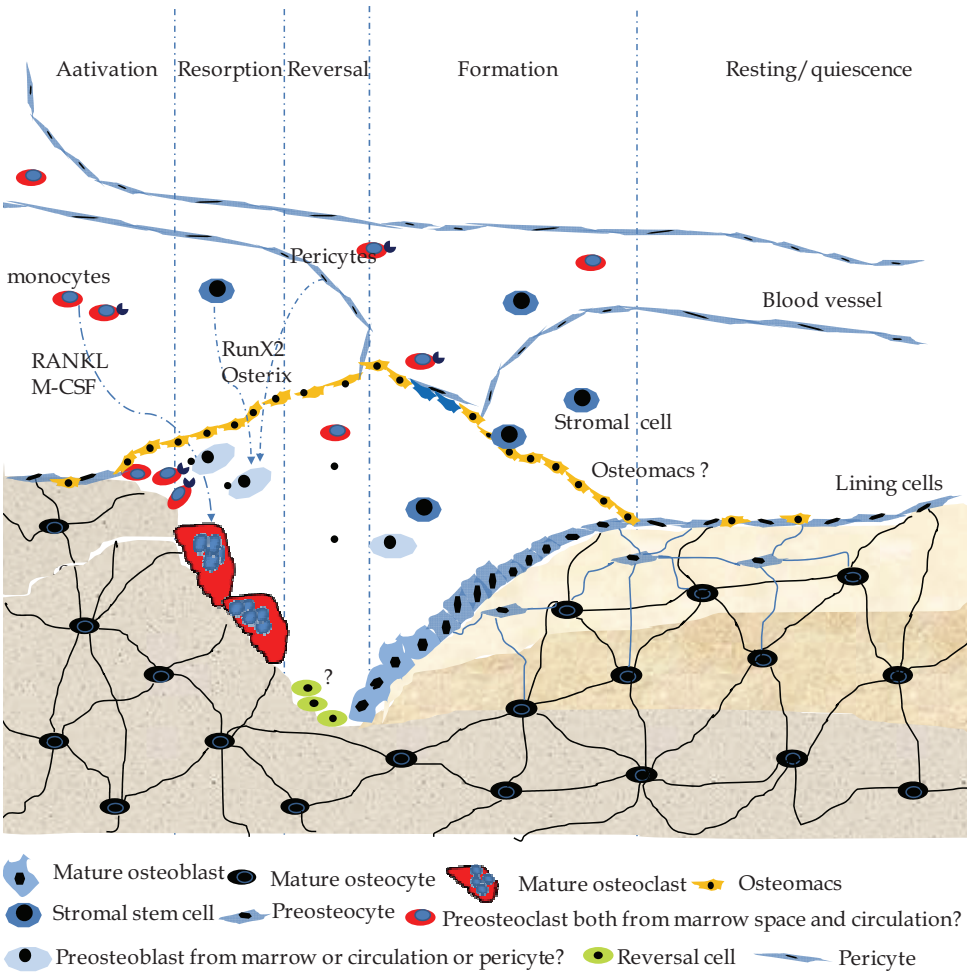


FIGURE 2 Schematic representation of a "basic multicellular unit (BMU)" and "bone-remodeling compartment (BRC)" in trabecular bone. Prior to activation, the resting bone surface is covered by bone lining cells intercalated with preosteoblast and osteomacs (osteomacrophage (Chang et al. 2008; Pettit et al. 2008; Winkler et al. 2010). Transforming growth factor-beta and osteoprotegerin inhibit the osteoclastogenesis. **Activation**, once osteocyte apoptosis due to micro-damage or demand for mineral ion takes place, lower TGF-β and higher PTH as well as other cytokines and growth factors stimulate lining cells detached and form the BRC together with adjacent capillary and osteomacs. BRC provides the structural basis for effective coupling and regulation of cellular activity (Eriksen 2010) both locally and systemically. Chemokines like monocyte chemo-attractant protein-1 and stromal cell-derived factor stimulate recruitment of monocytes, and cytokines like macrophage-colony stimulating factor and receptor activator of nuclear factor kappa-B ligand promote preosteoclast differentiation and resorption.

Resorption, mature osteoclasts attach on the bone surface and form a ruffled border and sealing zone to degrade the bone matrix. **Reversal**, via coupling factors, reversal cells stop bone resorption and clean the resorption pit preparing for new bone apposition by activated osteoblasts. **Formation** signals come from the degraded bone matrix, osteoclasts, or possible reversal cells. During formation, most of osteoblasts stay on the osteoid surface, a few lag behind and become osteocytes. Once the equal quantity of resorbed bone has been achieved, the osteoblasts either undergo apoptosis or become lining cells. The bone surface is restored to its resting/quiescent state and the remodeling cycle ends.

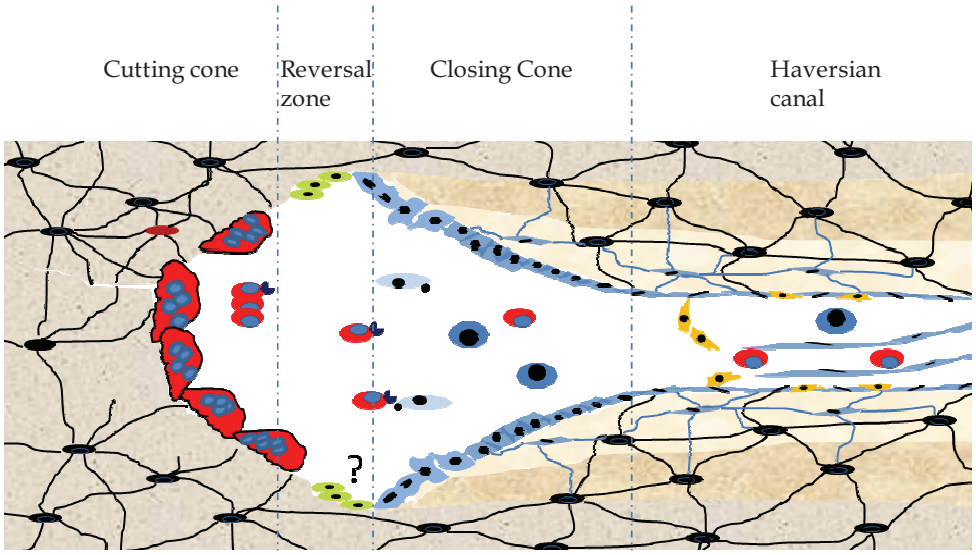


FIGURE 3 A "basic multicellular unit" and "bone-remodeling compartment" in cortical bone; for cell type description see Figure 2.

2.5 Mechanical properties of bone

Plausible contradictory functions of the skeleton, rigidity yet flexibility and lightness yet toughness, have been achieved during evolution by compromising among these demanding multiple functions (Currey 2003; Seeman and Delmas 2006; Chavassieux et al. 2007; Chappard et al. 2010). The mechanical competence of bone is determined by its material and its structural properties (Ammann 2003; Ammann and Rizzoli 2003; Davison et al. 2006). The strength of any bone and hence its ability to resist fracture is dependent on its mass/mineral density, trabecular /cortical microstructure and geometry as well as its material properties. Both experimental destructive/direct and image-based nondestructive/indirect methods are currently available to evaluate the mechanical properties of bone. However, we have to keep in mind that the

strength of the bone can be measured only by destructive testing in a laboratory to determine the force needed to break it.

Experimental tests provide both extrinsic and intrinsic parameters. Extrinsic parameters derive directly from load-displacement curves recorded during the test (Figure 4A). The initial straight line is called the elastic region, and it reflects the ability of the material to completely return to its original shape after deformation. The slope of this line indicates the material's extrinsic stiffness or rigidity, which is closely related to the mineralization of bone: the steeper the slope, the stiffer the material. If loading continues, the deformation is no longer proportional to the load, the elastic region ends and permanent damage begins; this point, correspond to the yield load, is called the yield point, and can be defined according to: 1) the point where the load-displacement curve begins to become nonlinear or 2) the point intersecting the curve, where a line parallel with the linear face of the curve and offset by 0.03% to 0.2% strain is constructed. After passing the yield point, the curve enters the plastic region; here the material begins to exhibit plastic properties and no longer returns to its original pre-deformation dimensions. As loading continues in this region, the material will eventually reach the ultimate load, reflecting the general integrity of the bone, at which point the specimen fails catastrophically. However, in some ductile materials like bone, due to their higher flexibility, after the ultimate load, the material may continue to deform until it reaches failure load and breaks. Work to failure (area under the curve) is the amount of energy necessary to break the bone. Ultimate displacement is inversely related to the brittleness of the bone. However, load-displacement often refers to complete structures (e.g., an intact femur/tibia) dependent on extrinsic features such as size and shape, which compromises the validity of the results for certain comparisons (Turner 2002; Turner 2006; Beaupied et al. 2007).

To overcome this limitation, intrinsic parameters are derived from extrinsic parameters and geometrical data, and describe bone tissue characteristics independent of the bone's geometry (Figure 4B). These include stress (yield, ultimate, and failure) and strain (stress = the load per unit area, N/m^2; strain = change in length over original lengthx100) as well as Young's modulus (the slope of the curve within the elastic region), reflecting the intrinsic stiffness of the material. Similarly, the area under the curve is a measure of the amount of energy needed to break the bone. This property of a material is called energy absorption or modulus of toughness, or just toughness, and can be measured by specialized techniques such as nano-indentation and acoustic microscopy (Rho et al. 1993; Turner 2002; Ritchie et al. 2008). The yield, ultimate, and failure stress the bone can sustain is called their corresponding strength. The amount of post-yield strain that occurs before the ultimate strength is reached is a measure of the material's ductility, reflecting its ability to resist the propagation of cracks. A ductile material is one that can change form without breaking; tendon is more ductile than bone. A brittle material is one undergoing little post-yield behavior before reaching ultimate strength; glass or ceramic is more brittle than bone.

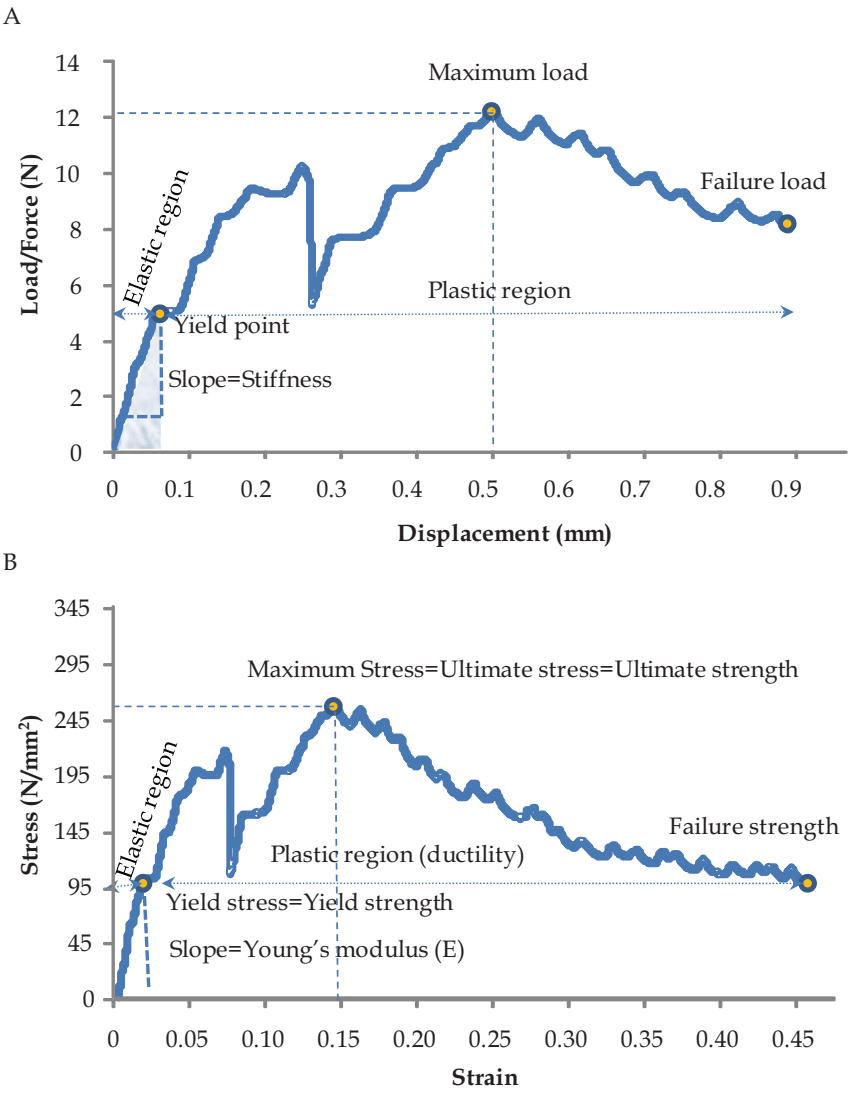


FIGURE 4 Representive load-displacement (A) and stress-strain (B) curves from mice tibia measured by a three-point bending machine.

The mechanical parameters can also be estimated from the geometrical properties of the bone combined with bone mass/mineral density, aided by a computer. Images of a bone provide adequate information about the bone's geometry, which is a major contributor to strength alongside density/mass. Generally, the loads exerted on the skeleton are a combination of compression and tension forces with bending and torsional moments. The highest stresses

experienced by the appendicular skeleton are due to these loading modes, and thus the resistance to bending and torsion loading is particularly important. The most efficient design for resisting bending and torsional loads is to distribute the bone material far from the neutral axis of bending and torsion. This axis can be quantified by a geometric term - the area moment of inertia (CSMI). Based on the CSMI, the section modulus as a strength surrogate can be calculated. This is inversely related to the maximum bending stress in the section (Bonnick 2007b). The methods currently available for skeleton imaging, such as DXA, CT, and MRI, offer the means for the nondestructive estimation of geometrical and/or mechanical parameters (Borah et al. 2001) (see Chapter 2.7).

2.5.1 Bone fragility, toughness, strength and quality

Bone fragility can be defined broadly as the susceptibility to fracture. From a biomechanical perspective, bone fragility includes at least three components: strength, brittleness, and work to failure. These parameters can be derived from a biomechanical test in which a bone specimen is loaded until it breaks. Bone strength (ultimate force) is defined as the highest point of the curve. Brittleness can be estimated from the reciprocal of the width of the curve (ultimate displacement), while work to failure is the area under the curve (Turner 2002).

Bone toughness is a measure of resistance to fracture and defined as the area under the stress-strain curve (energy to fracture). It is normalized work to failure and quantifies the amount of energy the tissue can absorb per cubic millimeter before failure, independent of the size and shape of the bone (Burr 2003). This energy is absorbed in three principle way: some energy is absorbed prior to the generation of a major crack in the form of diffuse damage, some for the requirement to start the final fracture crack, while the rest is required to drive the crack through in order to break the material (Zioupos and Currey 1998). Toughness can also be defined as the level of stress required at a crack tip to cause propagation of the crack (fracture toughness). Several parameters deriving from different fracture mechanics test methods, have been utilized to evaluate toughness including linear-/non-linear elastic fracture mechanics fracture toughness (Kc and Jc), and crack-resistance curves (R-curves) (Ritchie et al. 2008). Kc (critical stress intensity factor, MNm3/2) characterizes the stress intensity around the crack tip and reflects the toughness to initiate cracking, Jc (critical strain energy release rate, J/m^2) is related to the surface energy of the newly formed crack surfaces and includes the additional contribution from inelastic deformation (e.g., plasticity), and R-curves are obtained by plotting Gc (the strain-energy release rate, which is defined as the rate of change in potential energy per unit increase in crack area) *vs.* the crack length and reflects the toughness of a growing crack with the toughness of bone increasing as crack propagation advances (Wang and Puram 2004; Mullins et al. 2007; Ritchie et al. 2008).

Bone strength is a measure of resistance to permanent (plastic) deformation and is defined as the hardness or the yield, ultimate or fracture strength tested

in tension, compression, bending or shear. In most ductile materials, high strength implies low toughness and vice versa.

Bone quality is determined by material and structural properties coordinated by bone turnover. So far, this term is not well defined (Sievänen et al. 2007). Several properties are not directly dependent on bone mass. For instance, the size of bones and bone geometric properties, such as trabecular bone structure and utrastructure of bone are important determinants of bone strength.

2.6 Material and structural determinants of bone strength

Material basis

The mineral phase accounts largely for bone stiffness or rigidity while collagen provides bone's ductility or toughness. The relative ratio of mineral to collagen affects both bone strength and brittleness. An increase in the mineralization level leads to an increase in the stiffness of the bone: it becomes more brittle and less tough (Boivin and Meunier 2003; Davison et al. 2006; Turner 2006). The mean degree and distribution of mineralization in bone is similar in trabecular and cortical bone (Su et al. 2003), between genders and across age (Boivin and Meunier 2002b; Follet et al. 2004), and is mostly dependent on bone turnover activity (Boivin and Meunier 2002a; Boivin et al. 2009). However, it displays large heterogeneity in subjects who have bone diseases (Davison et al. 2006; Boivin et al. 2008). A reduced mineralization level also contributes to fragility (Boskey et al. 2005) indicated by low stiffness and strength (Hernandez et al. 2001) and low elastic modulus and yield stress (Burstein et al. 1975). Furthermore, mineral crystal size, number, and impurity all influence bone fragility; details have been reviewed in a recent article (Boivin et al. 2008). Generally, crystal size and perfection increase with ageing, the age-related increase in crystallinity causes increased brittleness, and crystal size in osteoporotic bone is also increased (Boivin et al. 2008).

The collagen phase mainly influences bone post-yield properties, i.e., ductility and toughness, and it also has some indirect effects on stiffness. An increment in collagen content is obtained at the cost of a decrement in mean degree of mineralization, as more protein is present in the matrix, collagen fibril size and orientation limit crystal size and orientation. Collagen decrement also dramatically influences bone mechanical properties. The best model in this case is *osteogenesis imperfecta* (OI) which involves mutations in the type I pro-collagen gene. Collagen dematuration decreases the bone's toughness and overall strength, while having minimal effects on the elastic modulus (Wang et al. 2001; Fantner et al. 2004). Further, collagen also inhibits crack propagation, decreasing the probability of micro-crack coalescence and fracture. Collagen cross-link formation affects the tensile strength and post-yield properties of bone (Paschalis et al. 2004; Garnero et al. 2006). Recent studies indicate that enzymatic and advanced glycation end products affect bone toughness and

stiffness as well as the elastic modulus, independent of the mineral phase and micro-architecture (Ruppel et al. 2008; Saito and Marumo 2010).

In addition to major inorganic mineral and organic collagen constituents, water and its role as the third most important component in bone tissue should not be ignored. It is known that in dehydrated bone specimens, stiffness and strength increase but toughness decreases (Wang and Puram 2004). Currently, two types of water, "mobile water" and "bound water", can be distinguished and measured by solid NMR (Wilson et al. 2005; Wilson et al. 2006; Nyman et al. 2008; Techawiboonwong et al. 2008). Loss of the water associated with the collagen phase decreases the toughness of bone, while loss of water in the mineral phase decreases both bone strength and toughness (Nyman et al. 2006). Later, the same group reported that strength and work to fracture of bone associate with bound water while the modulus of elasticity correlate with mobile water (Nyman et al. 2008). Fracture toughness and work to fracture of dehydrated bovine bone have been shown to be significantly decreased (Yan et al. 2008).

Structure

Structure and micro-architecture are determinant aspects of bone strength and also essential elements for the assessment of bone mechanical properties (Dalle Carbonare and Giannini 2004; Brandi 2009). The main structural determinants of bone mechanical strength include cortical thickness and porosity, and trabecular shape, thickness, connectivity, and anisotropy, as well as overall bone properties. Micro-architecture seems to be a determinant of bone fragility independent of bone mineral density (Dalle Carbonare and Giannini 2004). The bone cross-sectional area or size is positively correlated with the load-bearing capacity of the bone. Compression, bending, and torsion are the most common forces loaded on the skeleton during daily activity. The parameters describing cortical geometrical properties include cortical thickness, porosity, pore volume, number, area, and diameter (Kingsmill et al. 2007). Cortical pore diameter and the fraction of porous structures in femoral cortical bone from the mid-diaphysis negatively associate with yield stress and modulus (Wachter et al. 2002). The porosity of bone increases significantly with age, followed by the deteriorated mechanical properties; the increase in porosity accounts for over 75% of the reduction in strength of the proximal femur (McCalden et al. 1993). Morphological parameters including porosity, osteon density, osteonal area, osteonal lamellar area, osteon size, and Haversian canal size together can explain 49%-68% of the variation in fracture toughness of the human femur and tibia (Yeni et al. 1997).

In addition to BMD (Ulrich et al. 1999; Nazarian et al. 2007), the 3D-micro-architecture can improve the estimation of the mechanical competence of bone and the diagnosis of osteoporosis. Ultimate compressive strength of the lumbar vertebra was positively correlated with trabecular bone volume fraction (BV/TV) and trabecular thickness (Tb.Th) (Dempster et al. 1993). Yield strength in the rat lumbar vertebrae trabecular bone was strongly related to its BV/TV,

trabecular structure model index (SMI) and trabecular pattern factor (Tb.Pf) (Ito et al. 2002). BV/TV alone explained 84-94% of the variation in stiffness (Kinney 1999) and serves as the best predictor of Young's modulus (Ding et al. 2002). Trabecular number (Tb.N) has been shown to have a much greater impact on bone strength compared to Tb.Th (Silva and Gibson 1997). However, under some conditions of mechanically testing entire bones, measurement of bone microstructure does not improve the prediction of certain bone strength parameters (Thomsen et al. 2002; Lochmuller et al. 2008). Therefore, the relationship between measured micro-structural parameters and mechanical properties remains to be elucidated.

Micro-crack

Micro-crack or micro-damage accumulation both in trabecular (Nagaraja et al. 2005; Wang and Niebur 2006; Wang et al. 2007b) and cortical bone (Schaffler et al. 1995; O'brien et al. 2005), preventing the bone from catastrophic fracture, is formed during normal functional or fatigued loading of the skeleton and then repaired through the coordinated process of bone remodeling (Schaffler 2003), thus preserving the integrity of bone. Bone micro-damage accumulates dramatically with age (Schaffler et al. 1995; Chapurlat 2009), but with clear interindividual differences (Burr 2003; Diab et al. 2006). Resistance to fracture can be improved by the formation of micro-cracks or micro-damage that prevents the propagation of existing cracks through dissipating excessive energy. But, apparently, the accumulation of micro-damage in any material or structure will reduce its elastic modulus. Numerous studies have shown that the accumulation of damage or crack inside bone affects bone mechanical competence (Burr et al. 1998), such as boen toughness (Norman et al. 1998; Burr 2003) and strength (Burr et al. 1997). However, although micro-crack has been proposed as a contributing factor to increased skeletal fragility with age (Burr et al. 1997; Chapurlat and Delmas 2009), the association between micro-crack accumulation and mechanical properties does not appear to be linear, and the relationship between its accumulation and fracture risk also remains unclear (Chapurlat 2009). Bone remodeling is responsible for the repair of damage, as proposed by Frost in 1960 (Fost 1960), a large amount of data has been accrued to support this notion (Burr et al. 1985; Burr 1993; Burr 2002; Schaffler 2003; Martin 2007; Burr and Allen 2008; Kennedy et al. 2008). Osteocytes are commonly regarded as the mechanosensors for detecting damage and activating remodeling process in bone (Lanyon 1993; Cardoso et al. 2009).

Bone remodeling

Bone remodeling influences almost all of the factors directly or indirectly determining bone mechanical competence, both materially and structurally. Consequently, the rates of bone turnover dramatically affect bone fragility (Martin 2003; Davison et al. 2006).

Although we can make lists of variables which influence the mechanical competence of the skeleton, we have to keep in mind that alterations in these material or architectural variables do not necessarily reflect the strength of

whole bone, for example, we cannot predict the structural functions from its cell- and molecular-biological features for a sophisticated organism (Järvinen et al. 2005). On the other hand, we have to recognize that bones are not designed to resist fracture under extreme conditions and that achieving a compromising balance between stiffness *vs*. strength, toughness *vs*. flexibility, and lightness *vs*. strength is essential for them to complete both mechanical and metabolic functions (Currey 2003; Martin 2003; Currey 2005).

2.7 Non-invasive measurement of bone mineral density, architecture, and strength

A variety of methods can be used to measure bone mineral density and macro-/micro-architecture, and these methods have been comprehensively reviewed. The list of these methods includes invasive/noninvasive, *in vivo*/*ex vivo*, ionized radiation/ non-ionized radiation based facilities (Link and Bauer 2002a; Genant and Jiang 2006; Cano et al. 2007; Cano et al. 2008; Griffith and Genant 2008; Adams 2009; Bauer and Link 2009; Bouxsein and Seeman 2009; Donnelly 2010). Currently, the methods available for quantitatively assessing macro-structure include x-ray based radiography and dual energy X-ray absorptiometry (DXA) as well as quantitative computed tomography (QCT), and nuclear magnetic resonance based magnetic resonance imaging (MRI). For the micro-structure of cortical and trabecular bone, except for invasive/destructive classical histomorphometry, noninvasive/nondestructive methods include high-resolution peripheral computed tomography (e.g, hrpQCT), micro-computed tomography (μCT), high-resolution magnetic resonance (hrMR) (Alberich-Bayarri et al. 2010; Folkesson et al. 2010), and micro-magnetic resonance (μMR) (Link and Bauer 2002).

Dual-energy x-ray absorptiometry is, by far, the most widely used technique for bone measurements both in clinics and trials as well as epidemiological studies, and serves as the gold standard for clinical assessment of fracture risk and osteoporosis diagnosis (Bouxsein and Seeman 2009). This technique measures the radiation attenuation of photons of two different x-ray energies which are selected to optimize the separation of the mineralized and soft tissue components of the skeletal site analyzed during radiation transmission (Blake and Fogelman 2010). Attenuation values are then converted to bone mineral content (BMC, g) based on a phantom; bone area can be calculated by summing up the pixels within the projected bone edges. Subsequently, the "areal" bone mineral density (aBMD) (g/cm^2) is derived from the ratio of BMC and bone area (BA) (Blake et al. 1999). Since the DXA image is a projection (2D) of a three-dimensional object, the depth data on the skeleton is missing and the density is only "areal", rather than the true, volumetric density. However, based on the image processing and a few assumptions (Martin and Burr 1984; Bonnick 2007b), these 2D images also can be used to derive the geometrical and strength

parameters of bone, such as the cross-sectional area, section modulus and buckling ratio (Sievänen 2000; Genant et al. 1996; Beck 2007; Bonnick 2007b; Beck 2009b; Griffith et al. 2010). This analysis method termed 'Hip Structure Analysis (HSA)' extends DXA beyond aBMD. Since numerous assumptions have been used for HSA (Bouxsein and Karasik 2006; Beck 2007; Bonnick 2007b), the reliability and accuracy of the method in the estimation of bone strength is compromised and its application in clinics or experimental research is limited. Thus, for the purpose of predicting fracture risk, these derived parameters do not appear better than a DXA measurement of aBMD alone (Bonnick 2007a).

The preferred anatomical sites for DXA measurement include the lumbar spine, the proximal femur, and the whole body (Albanese et al. 2003; Andreoli et al. 2009), but peripheral sites can also be scanned. Advantages of DXA measurements include low radiation exposure (Damilakis et al. 2010), excellent precision, low cost, ease of use and short measurement time. However, due to the 2D nature of the scan, the measured mineral density (aBMD) is size-dependent; thus for clinical diagnosis, it is more accurate and precise for assessment of the mature skeleton. Hence caution should be executed in the case of children because of the large changes in body and skeletal size during growth (Bonnick 2002; Sanchez and Gilsanz 2005; Wren and Gilsanz 2006). DXA fails to distinguish cortical and cancellous bone and is unable to assess their 3D architecture. Therefore, although DXA currently serves as the gold standard for the clinical assessment of fracture risk, like all other facilities, its drawbacks should not be neglected. No information is provided by DXA on the bone material or geometric properties which are the true determinants of bone structural properties (Ferretti et al. 2001) .

Quantitative computed tomography utilizes X-rays and provides the 2D and 3D images which are based on the linear x-ray absorption coefficients of the tissues. Owing to the quantitative capacities of QCT in skeleton research, QCT is an early player in bone densitometry. However, the higher radiation dose (Griffith and Genant 2008; Adams 2009; Damilakis et al. 2010) and limited utility of QCT in epidemiological and pharmaceutical studies, compared to DXA, means that QCT has been little applied (Adams 2009). Since the 1990s, the need to separate the determinants of bone strength (e.g., BMD, trabecular /cortical bone) has given QCT a new lease of life in this field (Engelke et al. 2008). Unlike DXA, in QCT, the x-ray source and detector synchronously rotate around the subject. The acquired shadow images (matrix of attenuation coefficient) are reconstructed into 2D cross-sectional images and further to 3D images by using different algorithms and models.

Use of the mineral phantom allows the estimation of size-independent volumetric bone mineral density (vBMD) for trabecular and cortical bone, respectively. Besides vBMD, other important geometrical and biomechanically relevant assessments, such as cross-sectional moment of inertia and finite-element analyses, can be derived from these images (Genant and Jiang 2006). However, it should be noted that bone marrow fat content, a major determinant for the precision and accuracy of QCT bone densitometry, is much lower in

children, and thus the measurements are much more precise and accurate than in adults (Gilsanz 1998). Concerning the prediction of fracture risk, there is no consistent evidence on whether QCT performs better than DXA (Bouxsein and Seeman 2009). QCT scanners are also expensive, demanding for maintenance and technical support of proper function, and uneasy accessibility. These disadvantages have been partially overcome by the development of portable peripheral quantitative computed tomography (pQCT).

As its name implies, pQCT is limited to the measurements of the peripheral skeleton sites, including the upper and lower limbs *in vivo*. True quantitative morphological imaging of the trabecular or cortical architecture can be achieved by high-resolution pQCT (Nishiyama et al. 2009; Kirmani et al. 2009b; Burghardt et al. 2010; Goldenstein et al. 2010; Macdonald et al. 2010). QCT devices provide a wide range of spatial resolutions: clinical whole body QCT has an in-plane spatial resolution of up to 200 µm with a slice thickness of about 500 µm; recent high resolution pQCT achieve isotropic spatial resolution in the order of 80µm *in vivo* (Kirmani et al. 2009; Nishiyama et al. 2009); *in vivo* µCT systems are able to image bone with spatial resolutions of a few µm; synchrotron µCT and nanoCT systems can even obtain spatial resolutions lower than 1µm (Bauer and Link 2009).

Micro-computed tomography, in its resolution for structural analysis, is comparable to classic histomorphometry (Engelke et al. 1999; Barou et al. 2002; Cooper et al. 2003; Arlot et al. 2008; Gielkens et al. 2008). Currently an X-ray tube-based polychromatic system (Ritman 2004) and an synchrotron-based monochromatic system (Bonse and Busch 1996) are used *in vitro* to measure small bone biopsies from animals (Schneider et al. 2007b) and humans (Arlot et al. 2008; Recker et al. 2009; Chen et al. 2010a). *In vivo* µCT system also recently became available for small animal imaging (Laib et al. 2001; Paulus et al. 2001; Morenko et al. 2004). Compared to QCT, the radiation source and detector is fixed but the sample holder rotates around the central axis at certain angle intervals. Similarly to QCT, these two systems measure the radiation attenuation coefficients and the adopted algorithms then convert them to 2D cross-sectional images, while the subsequent 3D algorithms make real 3D visualization and analysis available. From these high resolution images, the parameters for the description of mineral density (Burghardt et al. 2008), trabecular architecture (Yamashita et al. 2000; Chappard et al. 2008; Sabsovich et al. 2008), and cortical porosity (Laib et al. 2000; Bousson et al. 2004; Cooper et al. 2004; Basillais et al. 2007; Borah et al. 2010), and strength (Cooper et al. 2007; Ural and Vashishth 2007) can be derived without stereological assumptions.

High resolution QCT (pQCT and µCT) is capable of describing bone mass and volumetric mineral density as well as spatial distribution, which reveals some aspects of the material and geometric properties determining actual bone strength. Compared to DXA or ultrasonometry, these methods provide more complete information on bone material, geometric and structural properties, their interrelationships, and their natural interaction with mechanical loads (Ferretti et al. 2001; Moisio et al. 2003). From 2D slices, besides geometrical

parameters, multiple strength indices can be calculated, which include the bone strength index (BSI) - a reliable predictor of the actual bending strength, stress-strain index (SSI) - a more general predictor of long bone strength (Gasser 1995; Ferretti et al. 2001), and compressive stress index (CSI) - a surrogate for compressive stress at the metaphyseal site (Kontulainen et al. 2008). From 3D images, several structural parameters can be acquired to quantify the trabecular architecture, e.g., BV/TV, Tb.N, Tb.Th, SMI and Tb.Pf as well as degree of anisotropy (DA) (Cano et al. 2007), and cortical properties, such as cortical porosity density, pore size, pore number, and distribution (Cooper et al. 2004; Bousson et al. 2004; Cooper et al. 2007; Basillais et al. 2007; Brandi 2009). Obviously, combining all these related parameters together would provide a better description of bone properties. Finite element analysis, recently introduced into this field, is regarded as a promising tool providing good estimations of whole bone strength (Cano et al. 2008). Due to the high demanding for computation tasks, this method so far is mostly limited to the laboratory experiments. However, it will be possible in the future to combine bone geometry with material characteristics and other possible parameters, e.g., physiological indices such as temperature, pH and concentration of ions (Kubicek and Lukes 2010).

Besides the aforementioned ionized-radiation based techniques, the non-ionized-based methods, such as MRI and quantitative ultrasound (QUS), also have their place in clinics and basic research on skeletal imaging. MRI/μMRI is a multifunctional facility capable of measuring bone structure and function (bone physiology) including bone architecture, marrow fat content, marrow perfusion and diffusion (Jiang et al. 2000; Borah et al. 2001; Griffith and Genant 2008). Recent solid-state MRI, by using the resonance signals of the phosphorus (^{31}p) constituent of the bone mineral phase, is a promising tool to noninvasively determine bone matrix properties (including degree of mineralization, collagen content, and inorganic/organic density) (Anumula et al. 2006; Wu et al. 2007; Bouxsein and Seeman 2009; Anumula et al. 2010; Cao et al. 2010). Generally, MRI measures the resonant signals from excited hydrogen protons (not just limited to hydrogen protons) within a strong magnetic field to generate 3D images (Cao et al. 2010). Images of bone tissue have a grayscale level (near-black) close to background noise. This gray value for mineralized tissue resembles that of the air bubble in the sample, and thus under this condition, image segmentation is extremely difficult (Cano et al. 2007). QUS is a relatively portable, easy to use, inexpensive and safe facility method. It measures the ultrasound beam attenuation, known as broadband attenuation (BUA, dB/MHz), and the speed of transmission, known as the speed of the sound (SOS, m/s) (Griffith and Genant 2008). Bone mineral density and other factors, such as structural parameters and elasticity affect BUA and SOS (Bossy et al. 2004; Haiat et al. 2009). QUS is commonly used to perform bone measurements at the calcaneus, less frequently at the patella, tibia, and phalanges of the hand (Gilsanz 1998; Sakata et al. 2004).

Other techniques
Collagen fibril architecture and organization can be observed and measured by circularly polarized light (Bromage et al. 2003), scanning acoustic microscopy (Hofman et al. 2006; Raum et al. 2006), electron microscopy (Su et al. 2003; Zizak et al. 2003; Lange et al. 2004; Rubin et al. 2004; Nalla et al. 2005; Suvorova et al. 2007), and atomic force microscopy (AFM) (Hassenkam et al. 2004; Bozec et al. 2005b; Haupt et al. 2006). Bone mineral composition can be measured by back-scattered electron imaging and crystallite size by X-ray diffraction (XRD) (Utku et al. 2008). It is also possible to combine multiple methods to assess bone mineral and matrix properties (Boskey 2006). For examples, AFM can be used to measure collagen shape, size of bone mineral (Eppell et al. 2001; Tong et al. 2003; Bozec et al. 2005a), collagen fibrils (Graham et al. 2004; Wallace et al. 2010), morphology of the lacunar-canalicular network (Reilly et al. 2001; Lin and Xu 2010;), bone cells (Lehenkari et al. 2000; Docheva et al. 2008), force and strain of bone (Thurner 2009) and other types of cells (Charras et al. 2001; Charras and Horton 2002a; Charras and Horton 2002b), the properties of the remodeling imprint (Hassenkam et al 2006), resorption cavity (Bozec et al. 2005b), and fracture behavior (Hassenkam et al. 2004; Hansma et al. 2005; Hassenkam et al. 2005). An another widely used method in bone material studies is Fourier transform infrared imaging micro-spectroscopy (FTIR), which is capable of determining the mineral/matrix ratio, the carbonate/phosphate ratio, crystallinity, and collagen maturity (collagen cross-link ratio) (Courtland et al. 2008; Boskey et al. 2009; Gourion-Arsiquaud et al. 2009; Lindgren et al. 2010).

These very high-resolution methods provide a possibility to assess micro- and even nano-level mechanical properties of bone and visualize real-time fracture behaviors combined with mechanical testing instruments (Hengsberger et al. 2001; Pathak et al. 2011). Nano-indentation, revealing tissue hardness and the elastic modulus, is able to measure the mechanical properties of micro-architectural features, such as osteons, lamellae and individual trabeculae, collagen fibrils, and individual mineral crystal (Fischer-Cripps 2002; Xu et al. 2003; Norman et al. 2008; Thurner 2009). Discernable variations in these measured indentation parameters have been found both in animal (Zhang et al. 2002; Tai et al. 2005; Donnelly et al. 2006; Middleton et al. 2010) and human bone specimens (Hengsberger et al. 2002).

2.8 Factors influencing bone properties

2.8.1 Intrinsic factors

Heritability of bone properties
Twin and family studies have shown that the heritability of bone properties, such as areal or volumetric bone mineral density (Wang et al. 2007a), skeletal geometry (Liu et al. 2004; Duren et al. 2007), and bone turnover (Harris et al. 1998) as well as ultrasound properties of bone (Howard et al. 1998; Danielson et

al. 1999; Hunter et al. 2001), accounts for a broad range (from 19 to 95%) of bone traits, depending on the skeleton sites measured by different methods and the models used for controlling the other conflicting factors (including both intrinsic and extrinsic factors) (Peacock et al. 2002). The heritability of bone properties, including BMD and geometry, may differ between men and women (Brown et al. 2004; Lenchik et al. 2004; Liu et al. 2004; Duren et al. 2007; Tse et al. 2009), anatomical regions (Jian et al. 2005; Wang et al. 2007a; Tse et al. 2009), and cortical and trabecular bone (Wang et al. 2007a; Cvijetic et al. 2010). Most of studies on the estimation of heritability have focused on areal BMD derived from DXA-based 2D images, thus the result is highly size- or geometry-dependent. With respect to the difference in skeleton site and age as well as gender, the degree of heritability of aBMD does not show consistency across studies, and thus both differences and similarities in the degree of heritability between axial and peripheral skeletons (Harris et al. 1998; Howard et al. 1998; Lenchik et al. 2004; Jian et al. 2005; Tse et al. 2009; Cvijetic et al. 2010), between weight-bearing and non weight-bearing skeletons (Wang et al. 2007a) as well as between the skeleton of children, adults and elderly persons (Dequeker et al. 1987) exist. For total body BMD, over 80% of the variance may be attributed to heritability (Howard et al. 1998; Bogl et al. 2011), and for BMD of the head 95% (Tse et al. 2009). However, in an earlier study, only 41% of total body BMD was attributed to heritability (Jones and Nguyen 2000). Males have been shown to have lower, higher or similar heritability compared to females at certain skeleton sites (Brown et al. 2004; Tse et al. 2009). Although current techniques are able to separate trabecular and cortical volumetric BMD, these do not improve the estimation of heredity (Lenchik et al. 2004; Havill et al. 2007; Wang et al. 2007a).

The heritability of geometrical parameters and the bone strength has been less investigated in humans. A few studies have reported that around 30-71% of the variance in bone size (Liu et al. 2004) and cortical thickness (Duren et al. 2007) can be attributed to heritability (Kiel et al. 2007). The estimated heritability of HSA-derived hip phenotypes has been shown to be between 40-84% (Streeten et al. 2008). In a recent pQCT-based twin study, heritability of the compressive strength index at both the distal radius and tibia has been estimated and shown a higher value at the distal radius (83%) than the distal tibia (61%) (Mikkola et al. 2008). Even fewer studies on genetic influences on bone micro-architecture have been published; one recent animal experiment found that 15-51% of the variance in trabecular parameters was attributable to heritability (Bower et al. 2006).

Studies on the genetic contribution to age-related bone loss have shown that heritability accounts for 40-56% of bone loss in twin studies (Makovey et al. 2007; Zhai et al. 2009) and 18-44% of BMD changes in an unselected population (Shaffer et al. 2008). The estimated heritability of QUS parameters accounted for 53-74% of broadband ultrasound attenuation (Arden et al. 1996; Howard et al. 1998; Danielson et al. 1999; Hunter et al. 2001), 55% of velocity of sound (Howard et al. 1998), and 19-82% of speed of sound (Howard et al. 1998; Hunter

et al. 2001). Based on these results, both common (Howard et al. 1998) and different (Arden et al. 1996) sets of genes controlling BMD and QUS parameters have been proposed.

Bone mass, lean mass, and fat mass are under strong genetic regulation and interact with each other, and it is possible that they share both genetic and environmental factors (Nguyen et al. 1998; Nordstrom and Lorentzon 1999; Bogl et al. 2011). A recent study suggests that peak BMD is affected both by acquired body weight (bone mass, lean mass, and fat mass) and by genetic factors, and that lean mass and BMD may have more genes in common than do fat mass and BMD (Bogl et al. 2011). Numerous studies have reported an association between bone phenotype and groups of polymorphic candidate genes both in animal experiments (Klein 2002) and human studies (Johnson et al. 2009; Ralston and Uitterlinden 2010). Genome-wide linkage screen of bone mineral density (BMD) has found multiple trait loci associated with low BMD values (Kaufman et al. 2008). Estrogen receptor alpha (Xiong et al. 2005) and COL1A1 (Long et al. 2004) as well as other gene polymorphisms (Giroux et al. 2010) have also been shown to be related to bone properties. During the past decade, especially the Human Genome Project (HGP) has opened up the prospect of the identification of the genes that determine the bone phenotypes.

Age, gender, peak bone mass and strength

Generally, BMC and bone size increase steeply with age and achieve approximately 80-90% of peak values by late adolescence, level off in young adult life, with peak BMC attained at about 20-30s years (Matkovic et al. 1994; Haapasalo et al. 1996b; Rico et al. 1991; Rogucka et al. 2001), and then begin to decrease. BMD shows a similar pattern, but its peak value is generally achieved earlier than BMC (Teegarden et al. 1995; Lin et al. 2003), during the first three decades of life, after which it gradually declines during the fourth decade and continues to decline into extreme old age. Peak bone mass is an important determinant of bone mass and strength in later life, but the exact time point peak mass or volumetric density is reached varies by gender (Magarey et al. 1999), skeleton site (Bonjour et al. 1991; Geusens et al. 1991), and ethnicity (Orito et al. 2009). Some evidence supports the hypothesis that peak acquisition in bone mass takes place earlier in women than in men (Rico et al. 1992; Magarey et al. 1999). However, other studies show peak vBMD at the lumbar spine and femur occuring earlier in males than in females (Leung et al. 2004; Kadam et al. 2009; Boot et al. 2010).

Many factors influence the accumulation of bone mineral during childhood and adolescence, including heredity, gender, diet, physical activity, endocrine status, and sporadic risk factors such as cigarette smoking. In addition to these modifiable factors during childhood, evidence has also accumulated that fracture risk might be programmed during intrauterine life (Javaid and Cooper 2002). Epidemiological studies have demonstrated a relationship between birth weight, weight in infancy, and adult bone mass (De Bono et al. 2010). Maternal smoking, diet, and physical activity also appear to

modulate bone mineral acquisition during intrauterine life; furthermore, both low birth size and poor childhood growth are directly linked to the later risk of hip fracture (Cooper et al. 2006; Cooper et al. 2008).

Age-related bone loss is a major underlying cause of osteoporotic fractures in the elderly. Such bone loss results in increased porosity in cortical and trabecular bones, decreased mineralization, and ultimately increased fracture risk. The bone material properties of aging human bone have been shown to change significantly in terms of its strength, stiffness, and toughness in male and female adults (Ammann and Rizzoli 2003). Age-related bone loss is manifested not simply as a global loss of bone, but is characterized by a loss of trabecular connectivity and increased cortical porosity (Marcus 1991). Cortical bone loss involves thinning of the cortex from endosteal resorption (Iwamoto et al. 1998) and an increase in intra-cortical porosity (Chen et al. 2010b). Consequently, apparent mineral density also decreases, while the true mineral density remains constant with age in either sex (Bergot et al. 1990; Laval-Jeantet et al. 1983). Cortical BMD decreases from the periosteum to the midcortex to the endosteum in parallel with the increased porosity (Bousson et al. 2000). The increase in porosity is largely due to greater pore size rather than a larger number of pores (Stein et al. 1999; Bell et al. 2000). It is generally presumed that compensation for the reduction of bone strength by progressive endosteal bone loss in adults is provided by the continuing periosteal apposition of new lamellar bone (Szulc and Delmas 2007). According to this hypothesis, once the periosteal apposition rate becomes slower than the endosteal resorption rate, thinning of the cortex will occur, followed by bone distribution further from the centroid of mass, resulting in increased second and polar moments of area, as well as the cortical area of the section (Lazenby 1990; Wang and Puram 2004). However, due to the absence of reliable evidence, debate on this hypothesis continues (Szulc et al. 2006; Sievänen 2008).

The most important consequence of ageing is the decrease in trabecular volume and increase in the marrow cavity. BV/TV, Tb.N, Tb.Th, and connectivity density (Bergot et al. 1990; Chen et al. 2010b) are found to decrease, whereas DA, BS/BV, and trabecular separation (Tb.Sp) increase with age (Dempster et al. 1993; Ding et al. 2002). Over the lifespan, females undergo loss of BV/TV and Tb.N with an increase in Tb.Sp, while males begin young adult life with thicker Tb.Th and primarily sustain trabecular thinning without net changes in Tb.N and Tb.Sp (Khosla et al. 2006). Decreases in Tb.N have been shown to have a much greater impact on bone strength compared with decreases in Tb.Th (Silva and Gibson 1997). Therefore, the age-related changes in trabecular bone are associated with deteriorated trabecular structure. However, the alterations in trabecular structural basis are site- and gender-specific and adapt to their specific surrounding environments (Leppänen et al. 2008).

Body mass

Epidemiological evidence has established a close link between body mass (fat mass and fat free mass) and bone mass in humans (Iwaniec et al. 2009; Reid

2008). It is well established that obesity is inversely correlated with fracture risk (Galusca et al. 2008; Gomez-Ambrosi et al. 2008) and that higher body mass is associated with higher bone mineral density in load-bearing bone in adults (Felson et al. 1993; Bakker et al. 2003). However, in adolescents, the results are contradictory. Some studies report that overweight and obesity have positive effects on whole body bone mass and mineral density as well as dimensions (Leonard et al. 2004; El Hage et al. 2009b), and on bone mineral density at the total hip, the lumbar spine L2-L4 (Leonard et al. 2004; Cobayashi et al. 2005; El Hage et al. 2009a;) and the femoral neck (El Hage et al. 2010) as well as on bone mineral content in the lower and upper limbs (Stettler et al. 2008), including both the trabecular (Uusi-Rasi et al. 2010a) and cortical bone sites (Sukumar et al. 2010), suggesting a positive role of obesity on the growing bone (Clark et al. 2006; Clark and Tobias 2011). In contrast, others suggest that obese subjects have relatively weaker bone to bear their over-weighted body mass compared to their leaner counterparts in both humans and animals (Goulding et al. 2000; Goulding et al. 2002; Braillon and Serban 2007; Goseki-Sone et al. 2007). Weight loss does not compromise bone strength (Stettler et al. 2008; Uusi-Rasi et al. 2010b). However, at the other extreme it is clear that partial removal of body mass or weight-bearing activity, such as tail suspension in animal experiments, space flight, swimming or bed rest, result in bone loss accompanied by decreased bone strength and deteriorated micro-architecture (Giangregorio and Blimkie 2002).

Some studies show that bone geometric properties and mineral density adapt to lean mass or fat free mass (Bakker et al. 2003; Wetzsteon et al. 2008; Ducher et al. 2009a), while greater weight in the form of fat mass does not have additional effects (Petit et al. 2005), or has a negative effects (Janicka et al. 2007; Ducher et al. 2009a) on bone traits. Further studies in obese adolescents show that in boys fat mass is a negative determinant of whole body and L1-L4 BMD, whereas fat mass is a better positive determinant of whole body BMD than lean mass in girls (El Hage et al. 2009c) and in obese sarcopenic postmenopausal women (Aubertin-Leheudre et al. 2008). Visceral fat is a negative predictor of bone mineral density in the whole body and spine (Russell et al. 2010). Muscle mass and strength have been well documented as strong predictors of bone mass and strength (Suominen 2006; Beck 2009a; Cousins et al. 2010; Perrini et al. 2010).

Although these DXA or pQCT based studies provide valuable data to understand the relationships between body mass and bone properties, due to population heterogeneity and the statistical models used for adjusting the multiple confounding variables (lean mass, fat mass, body weight, height, maturation, gender, height, physical activity and calcium intake, standing height, body mass index, waist circumference, hip circumference, waist to hip ratio, fat-free mass, and so on) as well as other extrinsic and intrinsic factors, the results are inconsistent and not comparable. Therefore, the exact connection between body mass and bone mass remains unclear.

Hormonal levels and other intrinsic factors

Systemic or local hormones, cytokines and growth factors produced by the autocrine, endocrine, and paracrine way also influence the skeleton, and vice versa. Among these factors, PTH (Tylavsky et al. 2005; Canalis et al. 2007), estrogen, growth hormone (Lissett and Shalet 2000), and IGF-I or its receptor (Maimoun et al. 2010; Perrini et al. 2010) have been well recognized. During childhood and adolescence, the differences in the accelerated growth spurt and in the increases in body and bone mass (Braillon 2003) between males and females are mainly determined by the action of sex steroids (Federman 2006; Cooper et al. 2008). Growth hormone (Attie et al. 1990) and leptin (Rogol 2010) also influence the growth spurt and bone mass. Local and systemic factors together determine the differing tempo of growth in bone size, mass, and density (Bass et al. 1999; Kirmani et al. 2009). In the adult, bone homeostasis may be explained by the interactions of PTH, (Chen et al. 2003), 1,25 dihydroxyvitamin D, calcitonin, and the sex steroids. Estrogen deficiency has long been recognized as a major cause of bone loss after menopause (Heersche et al. 1998). A strong relationship between estrogen and bone mass in both elderly men and women has been established, serum estradiol level has been shown to correlate closely with bone mass and low level etradiol associates with increased hip fracture risk (Slemenda et al. 1997).

2.8.2 Physical activity and nutrition

Animal studies suggest that mechanical loading or physical activity increases cortical thickness (Hubal et al. 2005; Castillo et al. 2006; Zhang et al. 2006) and trabecular cross-sectional area and density (Warner et al. 2006). In concert with animal experiments, numerous human studies also have shown that physical activity is an efficient tool to improve or maintain bone quality (Berard et al. 1997) and exerts its effects on the skeleton more efficiently during growth period (Kannus et al. 1995; Lehtonen-Veromaa et al. 2000a; Lehtonen-Veromaa et al. 2000b). In fact, it has been established that physical activity in humans has a protective effect on bone mass and microstructure in old people in a site-specific manner (Daly and Bass 2006; Ilich and Brownbill 2008; Totosy de Zepetnek et al. 2009).

The frequency, duration, type, and strain rate and distribution of mechanical loading has been extensively investigated in relation to bone cell function in animals and in cellular trials. Mechanical loading has been shown to have direct effects on the osteogenic and osteoclastogenic potential of bone marrow mesenchymal stem cells in mice (Mori et al. 2003) and rats (Song et al. 2007; Nagasawa et al. 2008) and on osteoblast cell proliferation (Singh et al. 2007; Kadow-Romacker et al. 2009). Altered biochemical markers of bone turnover also have been observed to associate with physical activity (Nowak et al. 2005; Adami et al. 2008; DiVasta et al. 2009; Ishikawa and Sakuraba 2009; Maimoun and Sultan 2010). Furthermore, as we know, the balance between bone formation and resorption is determined by osteoblasts and osteoclasts, which

are the main participants during modeling and remodeling (Dunlop et al. 2009; Letechipia et al. 2010; Maimoun and Sultan 2010).

Physical activity and bone mass (areal bone mineral density)

Physical activity, such as weight-bearing exercise, has long been recognized to influence BMC. Earlier studies have shown that BMC in the radius (Huddleston et al. 1980), the humerus (Dalen et al. 1985; Bass et al. 2002), and the ulna (Kannus et al 1994) of the playing arm were greater than that in the non-playing arm in tennis players (Ducher et al. 2009b; Ducher et al. 2010). Long-term intensive tennis playing started during growth and maintained into adulthood (Haapasalo et al. 1998) has more dominant side-to-side differences in BMC in the humerus (Haapasalo et al. 1996) and at the distal radius (Ducher et al. 2006) than that started in adulthood or later. Long-term and intensive physical activity such as football (Uzunca et al. 2005), handball (Vicente-Rodriguez et al. 2004), basketball, volleyball, judo and weightlifting (Breban et al. 2010) has been shown to increase aBMD and BMC in the weight-bearing sites. Female boxers also had elevated aBMD in arm, leg, and spine (Trutschnigg et al. 2008).

More generally, participation in gymnastics and running (Lehtonen-Veromaa et al. 2000b), jumping (Linden et al. 2006), dancing (Yannakoulia et al. 2004; Matthews et al. 2006), and long-term school-based exercises (MacKelvie et al. 2003; Schneider et al. 2007a; Alwis et al. 2008a) has also been shown to increase aBMD and BMC at the weight-bearing sites, such as the femoral neck and lumbar spine, in a gender-, site-, and maturity-specific manner (Mackelvie et al. 2001; MacKelvie et al. 2004; Weeks et al. 2008). Meta-analysis demonstrated that high-intensity progressive resistance training was efficacious in increasing absolute aBMD in a site-specific manner in premenopausal women (Martyn-St James and Carroll 2006). In a review article, comprsing 15 training and 3 cross-sectional studies, dancing was shown to improve not only aerobic power, lower body muscle endurance, strength and flexibility, balance, agility, and gait, but also to improve older adults' lower body BMC and muscle power, as well as to reduce the prevalence of falls (Kannus et al. 2005) and cardiovascular health risks (Keogh et al. 2009).

Non-weight-bearing or non-impact exercise, such as cycling (indoor and outdoor), water aerobics or exercises, swimming, stretching, Tai Chi chuan and flexibility exercises, were also found to affect aBMD and BMC. Swimming, as a non-weight-bearing sport, has been considered to be insignificant in the maintenance of bone mass but a recent study shows that it has a positive effect on bone mass and bone metabolism, but only among male adolescents (Derman et al. 2008). Tai chi chuan exercise was shown to be associated with increased aBMD (Chan et al. 2004) and retarded bone loss (Qin et al. 2002) in postmenopausal seniors (Lui et al. 2008). Moderate exercise like walking was also found to positively associate with bone properties (Palombaro 2005; Kitagawa and Nakahara 2008).

Physical activity and cortical/trabecular bone density

It has been shown that in athletes, bone mineral density can be 10-40% higher than that in sedentary control subjects in loaded sites (Nikander et al. 2006). Previous studies have shown that the amount of physical activity associates with trabecular vBMD, but not with cortical vBMD both at the radius and tibia in young men (Lorentzon et al. 2005). In contrast, it was found in one study in postmenopausal women that leisure time physical activity was positively and significantly associated with bending cortical BMD at the midshaft sites of the radius and tibia, while no associations between trabecular bone parameters were found (Hamilton et al. 2010). In a 9-month controlled trial, Heinonen et al. (2000) showed that high-impact exercise had no effects on cortical BMD in growing girls. However, Liu-Ambrose et al. (2004), found resistance and agility training to increase cortical BMD in 75- to 85- year-old women, who are commonly osteoporotic individuals. Adult female swimmers had lower tibial cortical BMD compared to controls while male swimmers had similar cortical BMD compared to controls or jumpers (Liu et al. 2003). Due to the limited number of studies, effects of physical activity on cortical or trabecular BMD remain controversial.

Physical activity and bone geometrical properties

The biggest difference between athletes and those who do not participate in sports participation has been observed in the long bone geometry. Bone hypertrophy has been found in the forearm of tennis players (Jones et al. 1977; Dalen et al. 1985; Haapasalo et al. 1996; Bass et al. 2002; Ducher et al. 2009b; Ducher et al. 2010) and in the tibia of volleyball players (Rantalainen et al. 2010), runners (Smock et al. 2009; Deriaz et al. 2010), and Olympic fencers (Chang et al. 2009). The increment in cortical wall thickness and cortical cross-section area can be over 50 % (Heinonen et al. 2001; Nikander et al. 2005). Similar results, showing increased cortical CSA and cortical thickness at the tibial shaft, have also been reported in a high-impact and odd-impact athletes (Nikander et al. 2006), in a 16-month school-based physical activity in young boys (Macdonald et al. 2009), and in a population based study (Lorentzon et al. 2005). In a special case, a thicker metacarpal cortical index in the dominant hand of the middle-aged teachers and dentists has been observed (Vehmas et al. 2005).

Beneficial effects of physical activity on bone geometry were also reported for people with chronic stroke (Pang et al. 2006; Pang and Lau 2010) and for postmenopausal women (Uusi-Rasi et al. 2003), showing increased cortex thickness at the tibia after short term training. However, in recent two studies, no effects of physical activity on bone structure and geometry were reported (Alwis et al. 2008b; Greene et al. 2009).

Physical activity and bone microstructure

With respect to effects of physical activity on bone microstructural properties, because of the limited measurement techniques available, there have been rather few human studies so far. Under high-impact physical activity, such as during gymnastics training, female gymnasts have higher apparent BV/TV and

Tb.N, and lower Tb.Sp (in the proximal tibia than controls, suggesting the enhanced trabecular micro-architecture of weight-bearing bone (Modlesky et al. 2008). Later, in a cross-sectional, population-based study, Nilsson et al. (2010) reported that men with the highest physical activity strain score had higher tibial trabecular BV/TV and trabecular number than men with the lowest strain score. A recent study using Hr-pQCT indicates that up to 8% variance in Tb.N can be attributed to impact physical activity in adolescent males and females (McKay et al. 2011). This suggests that physical activity also modifies trabecular bone micro-architecture. No association between physical activity and cortical micro-architecture has been reported so far.

Physical activity and bone strength

The amount and regional distribution of bone mineral around the centre of mass ultimately determine overall bone strength. Thus, the ultimate purpose for engaging in physical activity is to optimize bone mass and geometrical structures. As mentioned above, bone strength cannot be measured directly *in vivo*; however, substitutes, such as density-weighted moment of inertia (maximum, minimum, and polar), and varieties of strength indices (bending or compressive) as well as other parameters, have been widely used. Physical activity has been shown to positively associate with the bone strength index (BSI) at the metaphysis of the distal femur and tibia, strength-strain index (SSI) at the diaphysis at the same sites in girls (Farr et al. 2010a), and with BSI and polar strength strain index (SSIp) both at the middle and distal tibia and radius in older men (Cousins et al. 2010). Physical activity also positively relates to femoral neck bone strength derived from DXA-HSA in pre- and early pubertal children (Macdonald et al. 2008b) and in children during the adolescent growth spurt (Forwood et al. 2006). However, one recent meta-analysis suggests that exercise can enhance bone strength at loaded sites in children but not in adults (Nikander et al. 2010).

In athletes, these effects are more evident. World-class female athletes participating in swimming and gymnastics have similar ulnar and tibial bending stiffnesses but higher values than their untrained controls (Liang et al 2005). Isokinetic training also increases ulnar bending stiffness and BMC in young women (Miller et al. 2007). Similarly, athletes habitually exposed to high or low training loads display a greater bone strength index (BSI, the product of volumetric cortical BMD and cross-sectional moment of inertia within a region of interest) at the distal tibia than controls in adolescent girls (Greene et al 2005). In another study, the same group shows that female but not male adolescent middle-distance runners have greater distal tibial BSI than controls, showing a gender-specific effect (Greene et al. 2006). Similarly, a school-based exercise intervention also showed gender-specific effects, where boys had greater BSI at the distal tibia and SSIp at the tibial shaft than controls but girls had similar values to those of their counterparts (Macdonald et al. 2007). Both female and male long-term jumpers had the highest polar moment of inertia and strength strain index of tibial shaft, female swimmers compared with controls had lower

values while male swimmers had values similar to those of controls (Liu et al. 2003). In one recent study, a 16-month school-based physical activity programme in boys led to increased anterior-posterior bending strength at the tibial shaft with elevated physical activity, indicated by increased Imax and thickened cortex in the anterior and posterior as well as medial direction, suggesting a non-uniform geometric adaptation to mechanical loading (Macdonald et al. 2009).

Physical activity, bone loss, and sustainability

Physical activity retards bone loss (BMD and BMC) at different skeletal sites, preserves bone health in adolescent elite rhythmic gymnasts with hypoleptinemia (Courteix et al. 2007), and promotes bone mineralization and growth in preterm infants (Schulzke et al. 2007). It has also been shown to prevent bone loss in premenopausal women with rheumatoid arthritis (Tourinho et al. 2008) and in adolescents with vitamin D deficiency (Constantini et al. 2009). Functional electrical stimulation cycling exercise preserves or increases aBMD at the distal femur, proximal tibia, and calcaneus as well as aBMD (Chen et al. 2005; Dudley-Javoroski and Shields 2008a) and vBMD (Dudley-Javoroski and Shields 2008b) at the distal tibia in spinal cord-injured patients. Regular leisure time physical activity such as walking may protect against fracture in middle (Englund et al. 2010) and older age (Sorock et al. 1988) and reduce the risk of fragility fracture (Feskanich et al. 2002; Michaelsson et al. 2007; Sievänen and Kannus 2007). Walking or Nordic pole walking can promote rehabilitation following sacral stress fracture in long-distance running female athletes (Knobloch et al. 2007).

Thorpe et al. (2006) found that higher levels of physical activity at baseline are protective against the risk of wrist fracture during a 25-year follow-up. Although regular physical activity has a beneficial effect on bone health, it may also increase the risk of fractures by increasing the incidence of injury (Romani et al. 2002; Appleby et al. 2008; Nikander et al. 2011), especially in adolescents (Clark et al. 2008; Goulding 2007) and at older age (Kettunen et al. 2010).

Long-term beneficial skeletal effects achieved by physical activity during early childhood have been shown to be partly maintained or sustained up to late childhood (Fuchs and Snow 2002; Gunter et al. 2008; Janz et al. 2009), adulthood (Kontulainen et al. 1999; Valdimarsson et al. 2005; Nordstrom et al. 2006; Nilsson et al. 2009), and old ages even with less intensive (Kontulainen et al. 2004) or terminated exercise (Nurmi-Lawton et al. 2004; Nilsson et al. 2008; Karlsson et al. 2008; Nilsson et al. 2009). Leisure time physical activity in adulthood also has been found to be positively associated with BMD 22 years later (Morseth et al. 2010) and a habitually active lifestyle in elderly men and women retarded their bone loss (Daly et al. 2008a). However, the beneficial effects of high intensity weight-loading exercise on BMD in older post-menopausal women are lost after exercise cessation (Englund et al. 2009). The skeleton constantly adapts to present physical activity levels. Thus, increased BMD due to previous high physical activity may not prevent osteoporosis in later years. These phenomena are more evident in retired athletes. In girls

playing soccer, intense exercise after puberty is associated with higher accrual of BMD, but decreased physical activity in both the short-term and long-term perspective is associated with higher BMD loss than in controls (Valdimarsson et al. 2005). Reduced physical activity corresponds with greater bone loss at the trabecular than the cortical bone sites in men (Tervo et al. 2009). Elite gymnastics maintaining moderate exercise after retirement continue to have stronger radial and humeral shafts with larger cortical cross-sectional area and bone size and higher bone mass and larger femur and tibia shafts, although only higher tibia trabecular BMD and content, suggesting that skeletal benefits are site-specific, with greater geometric adaptations (greater bone size) in the upper compared with the lower limbs (Eser et al. 2009). Former football players also had higher whole body, lumbar spine, femoral neck, and greater trochanter aBMD than controls (Lynch et al. 2007).

Physical activity, frequency, magnitude, and intensity

It is considered that skeletal mass in humans may respond to the degree of impact, the period, the frequency, or/and the daily duration of physical activity. Postmenopausal bone mass can be significantly increased by a strength regimen that uses high-load low repetitions (high magnitude and low frequency) but not by an endurance regime that uses low-load high repetitions, suggesting that peak load is more important than the number of load cycles in increasing bone mass in early postmenopausal women (Kerr et al. 1996). Similarly, magnitude but not frequency accounted for 7% of the differences in CSA in habitual volleyball players compared to matched peers (Rantalainen et al. 2010). In contrast, another study found that the frequency of high acceleration impacts during 6 months of training was positively associated with 12-month bone changes at the femoral neck, trochanter and mid-femur (Ahola et al. 2009), consistent with their previous study, where they found that the acceleration slope of exercise-induced impacts achieved in fast movement like running and jumping was positively associated with changes in the hip (Heikkinen et al. 2007).

Randomized control trials provide preliminary evidence that low magnitude, high-frequency mechanical loading in the form of vibration is anabolic to bone in children with disabling conditions (Ward et al. 2004). Futher studies have shown that optimized intensity and duration of daily vigorous physical activity for at least approximately 25 minutes may improve femoral neck bone health in children (Sardinha et al. 2008). The intensity of physical activity positively correlates with aBMD change at the proximal femur and femoral neck (Jämsä et al. 2006) and at the hip in premenopausal women (Vainionpää et al. 2006). Even increasing the intensity of moderate exercise as walking may be able to preserve or increase postmenopausal bone mineral density (Borer et al. 2007). Thus, it is not surprising that different types of physical activity display inconsistent bone responses (Bailey and Brooke-Wavell 2008; Pikkarainen et al. 2009; Tamaki et al. 2008; Young et al. 2007).

Physcial activity modulated by other factors

The association between physical activity and bone properties is also modulated by other factors such as calcium (Specker and Binkley 2003), vitamin D (Gentil et al. 2009), catechol-O-methyltransferase (COMT) genotype (Lorentzon et al. 2007a), serum estradiol (Lapauw et al. 2009), and estrogen levels (Devlin et al. 2010).

Calcium is a major component of mineralized bone; intuitively, we assume that calcium supplementation would benefit bone mineral preservation and accrual. Some studies also support this notion (Yin et al. 2010). Calcium supplementation together with additional exercises, compared to controls, resulted in 2-3% greater increase in BMC at the loaded sites (femur and tibia-fibula) in boys with adequate calcium intakes (Bass et al. 2007) and 6-20% greater increase in aBMD at the femoral neck in children with inadequate calcium intakes (Hemayattalab 2010). Calcium supplementation itself has also been shown to improve bone mineral accretion in adolescents (Winzenberg et al. 2006). However, other studies have found that calcium supplementation, compared to physical activity, does not have additional benefits for bone properties, either in BMD or geometrical properties in adolescents (Juzwiak et al. 2008; Ward et al. 2007), older men (Kukuljan et al. 2009), or pre- or post-menopausal women (Uusi-Rasi et al. 2002) as well as gymnasts (Ward et al. 2007) and tennis players (Juzwiak et al. 2008). In a meta-analysis (Winzenberg et al. 2006) which included 19 studies involving 2859 children, calcium supplementation had no effect on aBMD at the femoral neck or lumbar spine, and only a small effect on total body BMC (standardized mean difference 0.14, 95% CI 0.01 to 0.27) and upper limb aBMD (0.14, 0.04 to 0.24). However, after the supplementation ended, this effect persisted only at the upper limb (0.14, 0.01 to 0.28) and there was no evidence that sex, baseline calcium intake, pubertal stage, ethnicity, or level of physical activity modified the effect.

Vitamin D is a vital factor which facilitates absorption of calcium. Daily calcium and vitamin D supplementation promotes greater trabecular BMC and vBMD acquisition in preadolescent girls (Moyer-Mileur et al. 2003). Calcium- and vitamin D3-fortified milk has been shown to prevent endocortical bone loss and slow the loss in cortical vBMD in elderly men (Daly et al. 2006), and even after withdrawal of supplementation the skeletal benefits continue to be sustained (Daly et al. 2008b). Vitamin D sufficiency is associated with low incidence of limb and vertebral fractures (Nakamura et al. 2010) and low vitamin D status has an adverse influence on bone mass, bone turnover (25-hydroxyvitamin D [25(OH)D]), and muscle strength in adolescent girls (Foo et al. 2009). Vit K1 supplementation is also associated with higher BMD lumbar and femoral neck and lower resorption (Macdonald et al. 2008c).

Nutrition

Nutrition plays a vital role in optimizing peak bone mass during growth (Weaver 2008) and in the prevention and treatment of osteoporosis in postmenopausal women (Stransky and Rysava 2009) as well as retardation of age-related bone loss in elderly persons (Miggiano and Gagliardi 2005). During

the critical period of bone development in childhood and adolescence, a combined dietary-physical activity intervention leads to increased bone strength (Dogan et al. 2009; Leite et al. 2007; Nemet et al. 2006). Specific foods, such as fruits and seafood (Zalloua et al. 2007), a protein-riched diet (Budek et al. 2007; Chevalley et al. 2008), green and yellow vegetables (Fujii et al. 2009) have been shown to positively impact bone properties (Vatanparast et al. 2005). Nutrition, including dietary fat and restricted caloric intake, is related to changed molecular markers of bone remodelling (Seibel 2002; Watkins et al. 2000) and may contribute to the risk of bone-related disease (Tam et al. 2009). Diet high in saturated fat can adversely affect the bone mineralization in growing animals (Corwin et al. 2006). Diet components are also closely associated with obesity in both humans (Astrup et al. 2008) and animals (Dourmashkin et al. 2005).

2.8.3 Other extrinsic factors influencing bone properties

Smoking decreases aBMD of the lumbar spine and hip in elderly men (Tamaki et al. 2010) and vBMD and geometrical parameters at both the radius and tibia in young men (Lorentzon et al. 2007b; Taes et al. 2010), and increases hip fracture risk in postmenopausal women (Jenkins and Denison 2008). Both smoking status and duration of smoking are deleterious factors on the aBMD of the lumbar spine (Kuo et al. 2008). Similarly, in an animal study, tobacco smoke deteriorated some of the biomechanical properties of bone in growing female mice (Akhter et al. 2005). However, one recent study shows that the deleterious effects of smoking on tibial and radial bone mass and strength may diminish with age (Wust et al. 2010). Chronic ethanol consumption also has been shown to inhibit post-lactation anabolic bone rebuilding in female rats (Shankar et al. 2008).

There are plenty of drugs influencing bone metabolic and structural functions. Hormone replacement therapy (HRT) has been shown to be associated with increased bone mass and bone strength in postmenopausal women (Mikkola et al. 2011). Anti-diabetic drugs like glitazones decrease BMD and increase fracture risk (Rejnmark 2008). In a population-based cohort, antidepressant drugs have been shown to associate with decreased BMD (Mezuk et al. 2008). Oral contraceptive use in young women is associated with lower bone mineral density than that of controls (Almstedt Shoepe and Snow 2005). Although anti-osteoporosis drugs have been successfully used to prevent or retard bone loss and ultimately to improve the life quality of osteoporotic patients (Berecki-Gisolf et al. 2008; Eastell et al. 2009; Vujasinovic-Stupar et al. 2010), their side effects are also pronounced, including decreased bone toughness (Mashiba et al. 2000) and increased elastic modulus (Brennan et al. 2009).

Many disorders, such as obesity or diseases like rickets and osteomalacia (Unnanuntana et al. 2010), and prior fractures also affect bone properties (Järvinen and Kannus 1997; Farr et al. 2010b). It has been shown that impaired geometric properties of the tibia in older women are associated with hip

fracture history (Mikkola et al. 2007). One recent study shows that lower trabecular vBMD at the metaphyseal regions of weight-bearing bones is associated with prior fracture in young girls (Farr et al. 2010b).

2.9 Osteoporosis and obesity

Osteoporosis is a disease characterized by low bone mass and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures (Alexandre 1995; Delmas 2000; Roux 2001). Numerous studies have investigated the underlying mechanisms and ways of preventing it. Obesity is a condition of excessive body fat that causes or exacerbates the risk of developing non-insulin dependent diabetes, cancer, cardiovascular diseases, and other diseases, and that is associated with chronic inflammatory status (Weisberg et al. 2003). These two disorders of body composition have usually been considered separately, but more recently both clinical and experimental data have established a close link between them (Rosen and Bouxsein 2006). Epidemiological data and animal studies indicate that these two diseases share several features, including a genetic predisposition and a common progenitor cell (Gimble et al. 2006), and that both are influenced by nutrition and sedentary life styles (Jebb and Moore 1999). Furthermore, abundant evidence suggested that adipose tissue as an endocrinal organ affects bone metabolism through secreted adipokines (Gomez-Ambrosi et al. 2008). Whether these effects are protective or detrimental continues to be controversial (Reid 2008). Physical activity and nutrition have been shown to affect these two diseases; however, the mechanisms remain largely undetermined.

2.10 Summary of literature review

Bone is not an inert material; instead, like all the other organs/tissues, bones continuously modify and optimize their own properties through modeling and remodeling, responding to different local or systemic stimuli. Bone during the lifetime is influenced by the forces associated with gravity and physical activity; these are static loading and dynamic loading, respectively. Muscle forces are generally greater than the external forces acting on the body (e.g., ground reaction forces) (Judex and Carlson 2009) and create the peak loads on bone because of the body's poor muscle leverage (Murphy and Carroll 2003; Bass et al. 2005; Kohrt et al. 2009); that is, muscle attachments area generally close to the joint so they need to generate large forces on the bone to move the lever arm. It has been reported that both muscle mass and strength associate with bone properties as a major determinant of bone mass, geometry and strength (Suominen 2006; Daly et al. 2008) as well bone mineral density (Segal et al. 2008).

Although the influence of mechanical or non-mechanical factors in musculoskeletal development and functional adaptation has been widely considered, there is currently no consensus on this topic. Various hypotheses or theories have been proposed over the last hundred years. Among these, Harold Frost's "mechanostat" is the most popular. Later, he and his colleague (Frost 1996; Frost et al. 1998) further developed this theory to produce the Utah paradigm of skeletal physiology, the principles of which were described by Webster Jee in 2000 (2000). Specifically, Bass and Daly later discussed the effect of exercise and nutrition on the "mechanostat" (Bass et al. 2005). This theory describes how the skeleton adapts to mechanical stimuli (Turner 1998; Turner and Pavalko 1998) and other non-mechanical factors serve as a regulator (Jee 2000) (see Fig. 5).

As many of the results on the long-term effects on bone properties derive from observational studies including a selection bias, and very long-term exercise interventions are lacking. In this thesis, twin pairs discordant for physical activity were used to investigate the long-term effects of physical activity independent of genetic factors. Since the effects of mechanical loading exerted by body mass and physical activity on the microstructure of bone is not fully understood, diet-induced obesity and voluntary wheel running were employed to investigate effects of different mechanical loading on bone properties by using modern methodology to learn more about the adaptation of bone microstructure to mechanical loading.

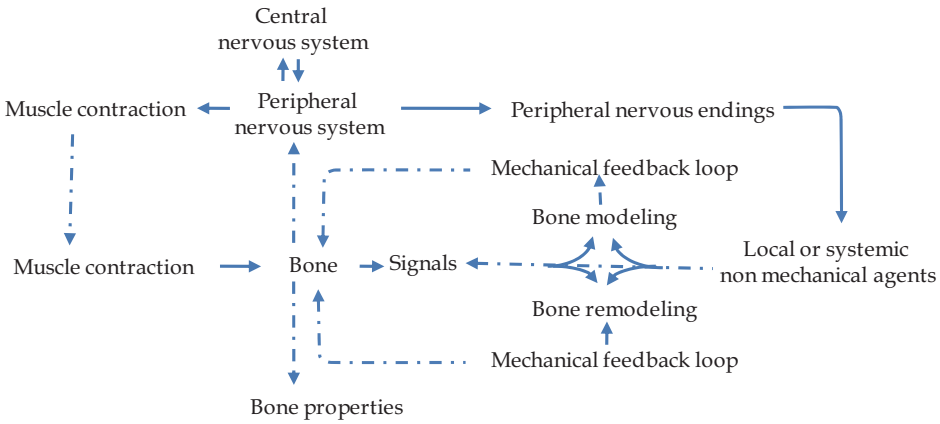


FIGURE 5 Schematic view of Utah paradigm of skeletal physiology. Modified from Jee (2000).

3 AIMS OF THE STUDY

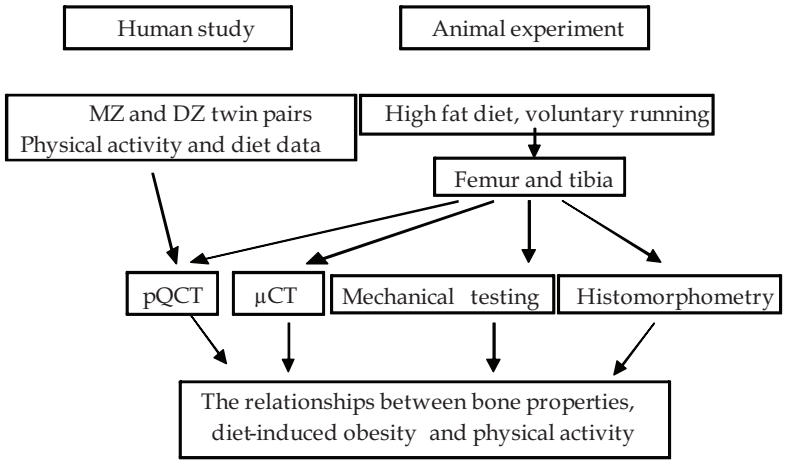
The general aim of this study was to elucidate the mechanisms of bone adaptation to physical activity and obesity. The study comprises two parts: a human study and an animal experiment (Figure 6A).

The specific aims of this study were twofold:

- To investigate how bone mineral density and geometrical properties adapt to long-term leasure time physical activity in a twin study. (I)

- To study the adaptations of bone micro-structural properties to diet-induced obesity, voluntary wheel running, and their combination. (II-IV, Figure 6B)

A



B

Analysis	article II	article III	article IV	thesis
pQCT	slice 3 and 5	slice 4	-	slice3 and s5
Mechanics	femoral neck	-	-	femoral neck, tibia, and L3
µCT	-	slice 4	1mm ROI	1mm ROI and L4
Histomorphometry	-	-	-	L4

FIGURE 6 Study design (A) and animal experiment publication (B).

4 MATERIALS AND METHODS

4.1 Human study (I)

A written informed consent was provided by the twins in accordance with the ethical committees of University of Jyväskylä, and the Central Hospital of Central Finland. The study was part of the "TWINACTVE" project (Leskinen et al 2009) and the population comprised 16 same-sex twin pairs of whom 7 were MZ and 9 DZ pairs drawn from the population-based Finnish Twin Cohort (I). Briefly, all pairs had persistent 32-y discordance in their leasure time physical activity habits. The same co-twin of twin pair was significantly more active at the baseline assessments (both in 1975 and 1981), in at least four out of six assessed time points (i.e. years 1980, 1985, 1990, 1995, 2000, 2005) of the retrospective follow-up interviews, and finally, at the follow-up assessment in 2007. The most common types of physical activity by the active co-twins were: walking (30% of total physical activity volume), jogging (11%), cross-country skiing (9%), forest/food work (7%), golf (6%), ball-games (6%), cycling (5%), gymnastics/dancing (5%), gym-training (4%), and different every-day activities such as gardening (17%).

In 2007, body weight and height were measured and body mass index was calculated by dividing body weight (kg) by height^2 (m^2). Self-reported weight and height were available from the baseline questionnaires.

pQCT densitometry

Bone properties were measured at 5% and 50% of the length of the tibia proximal to the distal end of the tibia by a pQCT device ((XCT-2000; Stratec Medizintechnik, Pforzhem, Germany) and the analysis of the obtained images was performed with the manufacturer's software package (version 5.40) and software designed for analyzing cross-sectional CT images (Geanie 2.1, Commit, Espoo, Finland) (for details, see original publication I).

A threshold of 280 mg/cm^3 for the mid-shaft of the tibia and 169 mg/cm^3 for the distal site was used to determine the outer bone border. At the tibia mid-

shaft, total cross-sectional area (CSA_{tot}) was defined as the area enclosed within the outer bone border. Separation of the cortical, sub-cortical/trabecular bone, and marrow cavity was performed using a contour detection algorithm with 710 mg/cm^3 (K-mode) to distinguish cortex from sub-cortical and trabecular bone and 100 mg/cm^3 to separate bone from marrow cavity. Total cross-sectional area (CSA_{tot}, mm^2), bone CSA(CSA_{bone}, mm^2), volumetric BMD ($vBMD_{bone}$, mg/cm^3), bone mineral content (BMC_{tot}, mg/cm), cortical CSA (CSA_{co}, mm^2), cortical vBMD ($vBMD_{co}$, mg/cm^3), cortical thickness (Th_c, mm), CSA_{co}/CSA_{tot}, bone marrow cross-sectional area (CSA_m, mm^2), and density weighted moment of inertia (Ipolar, Imax, and Imin excluding bone marrow) reflecting the bone's resistant to bending and torsion were determined from this bone site. In addition, BMC was expressed as the polar distribution of bone mass as a function of the angular distribution around its centre.

At the distal site, separation of trabecular and cortical bone was performed by peeling 30% from the outer edge of the bone's cross-sectional area and considering the remaining area as trabecular bone (S-mode). Total CSA (CSA_{tot}, mm^2), total volumetric BMD ($vBMD_{tot}$, mg/cm^3), total BMC (BMC_{tot}, mg/cm), trabecular volumetric bone mineral density ($vBMD_{trab}$, mg/cm^3), and compressive strength index (CSI = $vBMD_{tot}^2$ x $CSA_{tot}/10^8$ g^2/cm^4) were determined.

In addition, polar mass (BMC) and radial density distribution around the center of mass were calculated for both the midshaft and distal tibia. A threshold of 181 mg/cm^3 for the midshaft of the tibia and the distal site was used to determine the outer bone border.

Statistics

All data were checked for normality using the Shapiro-Wilk test. Paired t-test for normally distributed variables was used to evaluate differences in the bone parameters. For non-normally distributed data, the Wilcoxon signed rank test was used. The level of statistical significance was set at $p < 0.05$. Data were analyzed using SPSS 14.0 and Stata 8 software.

4.2 Animal study (II - IV)

This study was approved by the National Animal Experiment Board, Finland and has been described in original publication II. Briefly, 40 male 7-week-old C57BL/6J mice were randomly allocated into one of four intervention groups (10/group and 1/cage): control diet (C), control diet + voluntary wheel running (CR), high-fat diet (HF), and high-fat diet + voluntary wheel running (HFR). Animals in the CR and HFR groups were housed in custom-made cages with a running wheel with free access to the wheel 24 h/day for 21 weeks. C and HF animals were housed in similar cages without the running wheel. The mice had continuous access to the control or high-fat diet and regular tap water. The control diet was a standard rodent diet R36 (4% fat, 55.7% carbohydrate, 18.5%

protein, 3 kcal/g, Labfor, Sweden). The high-fat diet was a lard-based purified diet D12492 (60% fat, 20% carbohydrate, 20% protein, 5.24 kcal/g, Research Diets Inc., USA).

Body mass and food consumption were measured at two-week intervals. Feed efficiency over the intervention period was calculated as body mass gain per unit energy intake (mg/kcal) (II-IV).

Endurance running capacity was evaluated at week 16 of the intervention. All the mice were exposed to a forced maximum running test on a motor driven treadmill. The test was started at a speed of 10 m/min for 5 min against an incline of 0.8°. The speed was increased in 5-min intervals by 1m/min until exhaustion (II-IV).

For all the mice glucose tolerance and insulin tolerance test (GTT and ITT, respectively) were performed after a one-week interval on the 10- and 20-week intervention. Glucose level was determined by B-Glucose photometer (HemoCue AB, Angelholm, Sweden). Areas under the curve of GTT (AUC-GTT) and ITT (AUC-ITT) were calculated using the trapezoidal rule (II-IV).

The mice were injected with tetracycline (20mg/kg) and calcein (15 mg/kg) at intervals of 10 days and sacrificed 3 days after the calcein injection.

After 21 weeks of intervention the mice were sacrificed by cervical dislocation. Blood samples were collected and sera were separated after 1 hour of clotting, and stored at -70°C for further analysis. Levels of insulin, leptin, osteoprotegerin (OPG), osteocalcin, resistin, and plasminogen activator inhibitor-1 (PAI-1) in serum were measured using a Milliplex mouse bone metabolism panel (Millipore, USA) according to the manufacturer's instruction (II-IV).

The left femur and tibia of the hind legs were separated and trimmed of attached soft tissue and connective tissues, wrapped in phosphate-buffered saline-soaked gauze, and stored frozen at -20°C. The whole spine and the right femur and tibia were also harvested and fixed in 70% ethanol for further analysis.

pQCT densitometry

A pQCT apparatus (Stratec XCT Research SA, Stratec Medizintechnik GmbH, Pforzheim, Germany) calibrated using a hydroxyapatite standard cone phantom was used for the bone densitometry. A voxel size of 0.07x0.07x0.5mm was used for all measurements. The left femur was thawed overnight at 4°C and inserted into a specially constructed plastic syringe with the shaft in the axial direction. Four slices were scanned at the metaphyseal region at 0.5mm intervals starting from the 12.5% landmark and two slices from the 50% landmark for the diaphysis area (Figure 7). All the scanned slices were analyzed by bone analysis software (Geanie 2.1, Commit, Espoo, Finland). A contour-detecting algorithm (k-mode) with a threshold value of 500 mg/cm^3 was chosen for the separation of trabecular and cortical bone and 100 mg/cm^3 for marrow and bone separation. Bone traits from the slices 3 and 5 (s3 and s5) were described (II). The parameters reported for the diaphyseal region comprised total bone cross-sectional area (CSA_{bone}), total bone mineral density ($vBMD_{tot}$),

total bone mineral content (BMC_{tot}), cortical cross-sectional area (CSA_{co}), cortical bone mineral density ($vBMD_{co}$), cortical bone mineral content (BMC_{co}), cortical thickness (Th_c, using a ring model), marrow cross sectional area (mCSA), and density-weighted moments of inertia (Ipolar, Imax, and Imin). The parameters reported for the metaphyseal region comprised tCSA, tBMD, tBMC, trabecular cross-sectional area (CSA_{tra}), trabecular bone mineral density ($vBMD_{tra}$), trabecular bone mineral content (BMC_{tra}), CSAm, and moments of inertia.
The distribution of polar mass (BMC) and radial density (BMD) around the center of mass was described for both s3 and s5.

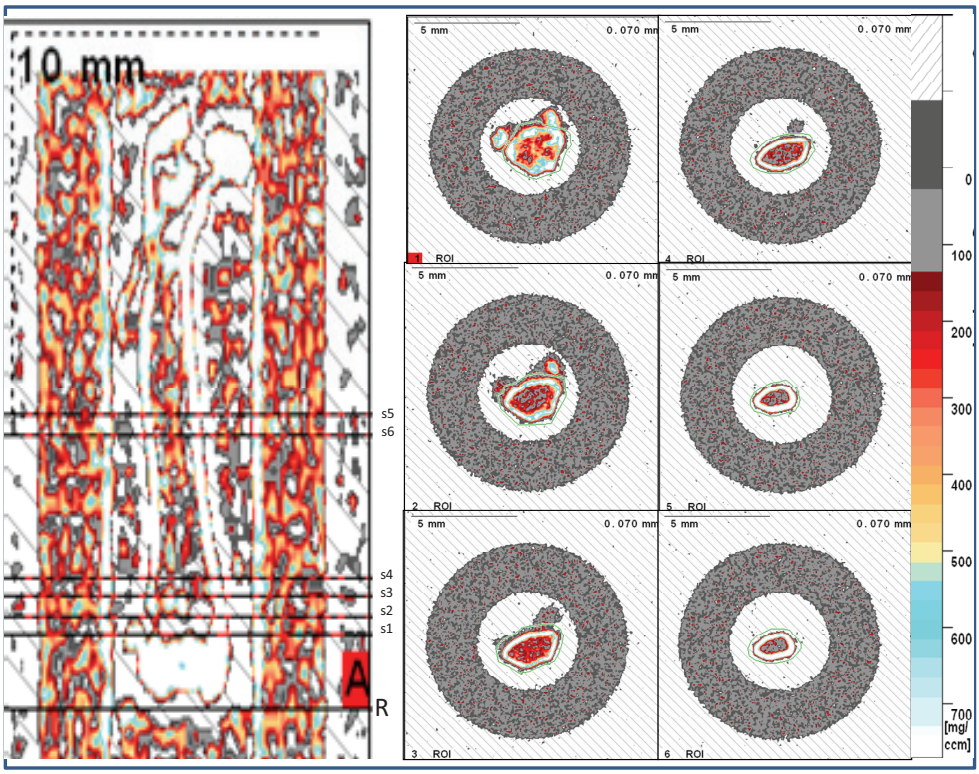


FIGURE 7 Four slices were scanned at the metaphyseal region at 0.5mm intervals starting from the 12.5% landmark and two slices from the 50% landmark for the diaphyseal region in the left femur (the results from s3 and s5 (II) as well as s4 (III) are reported in this thesis).

Biomechanical testing
After the pQCT measurement, a cantilever bending test of the left femoral neck was performed (Instron 3343, Massachusetts). Briefly, the proximal half of the left femur was fixed axially in a methylmetacrylate plate stage and compressed in a direction parallel to the femoral shaft axis at a constant speed of 4.5 mm/min (II), and the distal half of the femur was fixed in 70% ethanol for the

μCT measurement. After thawing at 4°C, the mechanical properties of the left tibia were also measured by using Instron 3343. The third lumbar vertebra (L3) was dissected from the spine and rehydrated. The mechanical properties of L3 were determined using a compressive test in MultiTest1-x (Mecmesin, West Sussex, UK). The tibia was positioned horizontally with the anterior surface upward, centered on the supports (span = 9 mm); and the middle point of the tibial shaft and the third lumbar vertebral body (L3) without the endplates of the cranial and caudal surfaces and processes were vertically compressed at a constant speed of 4.5 mm/min until failure. Each L3 vertebra was placed centrally on the flat and smooth surface of a steel column (Diameter = 25 mm) attached on the platform of MultiTest1-x and compressed by an upper crosshead (Diameter = 4 mm) in a direction parallel to the vertebral longitudinal axis.

The measured data from the femoral neck, the left tibia and L3 vertebra were recorded and converted to a load-displacement curve in a monitoring recorder linked to the tester. The peak load, displacement and energy at peak load, fracture load, displacement and energy at fracture load, and stiffness were calculated.

MicroCT measurements

The trabecular and cortical bone microstructure of the distal part of the left femur (III-IV) and the fourth lumbar vertebra were evaluated by using a Skyscan 1172 desktop scanner (Skyscan, N.V., Aartselaar, Belgium). The distal femur and L4 vertebra were scanned at a high resolution (2.8 μm) using an integration time of 400 ms, energy of 90 kv, and intensity of 112 μA. Projection images were acquired over angular range of 360° with an angular step of 0.4° and reconstructed by SkyScan's cluster reconstruction software (v.1.6) based on the Feldkamp algorithm and stored in 3-D arrays.

Segmentation of trabecular and cortical bone

For the distal femur, four regions (s1, s2, s3, and s4; Figure 7) were selected. Each region contained 174 cross-sectional images corresponding to the thickness measured by pQCT. For the cortical shell and trabecular structure analysis, we excluded s1, s2 and s3 due to their complicated structure (connection with fabella and condyle). The resulting grayscale images were binarized and filtered with an Accurate Gaussian Blur filter (sigma = 0.8) to reduce noise, and segmented from background using a simple global thresholding method (Buie et al. 2007; Dufresne 1998; Waarsing et al. 2004). The proposed algorithm was based on dilation, connection, erodation, and subtraction and all procedures were performed using ImgeJ (for details see Figure 8) (III).

In IV, using the same method, an another region of interest (ROI), excluding the primary spongiosa, commencing at a distance of 1.8 mm from the distal growth plate, and extending a further longitudinal distance of 1 mm (347 slices) in the proximal direction, was analyzed. Reconstructed bone images were filtered and binarized.

The acquired binarized image stack of trabecular bone was analyzed by using a CT-Analyser (version 1.6.1). Connectivity density (Conn.N, mm^{-3}), trabecular bone volume (BV, mm^3), surface (BS, mm^2), Tb.N, and Tb.Sp, as well as the BS over BV ratio (BS/BV) were calculated by the Mean Intercept Length (MIL). Tb.Th was calculated according to the method of Hildebrand (Hildebrand et al 1999). In addition to the computation of metric parameters, values of topological parameters were calculated to describe the 3D nature of the trabecular bone. Tb.Pf, representing the amount of concave (plate-like bone) and convex (rod-like bone) structures was calculated. The higher the Tb.Pf, the more rod-like is the shape of trabecular bone. SMI, measured for the prevalence of plate-like or rod-like trabecular structures, where 0 represents "an ideal plate", 3 "a rod or cylinder", and 4 "a sphere". The degree of anisotropy (DA) of a structure, defining the preferred orientation of trabeculae, was also calculated.

For the L4 vertebrae, by using CT-Analyser (version 1.6.1), a core cylinder centered through the vertebral body (Diameter = 0.9 mm), extending from the cranial to the caudal growth plates, was made. A volume of interest for the quantitative analysis of trabecular bone structure was defined as a 1 mm length (347 slices) in the middle region of the cylinder's long axis. Morphometric parameters, including Conn.D, BV, BS, Tb.N, Tb.Th, Tb.Sp, SMI, Tb.Pf, and DA were computed without assumptions regarding the underlying bone microstructure.

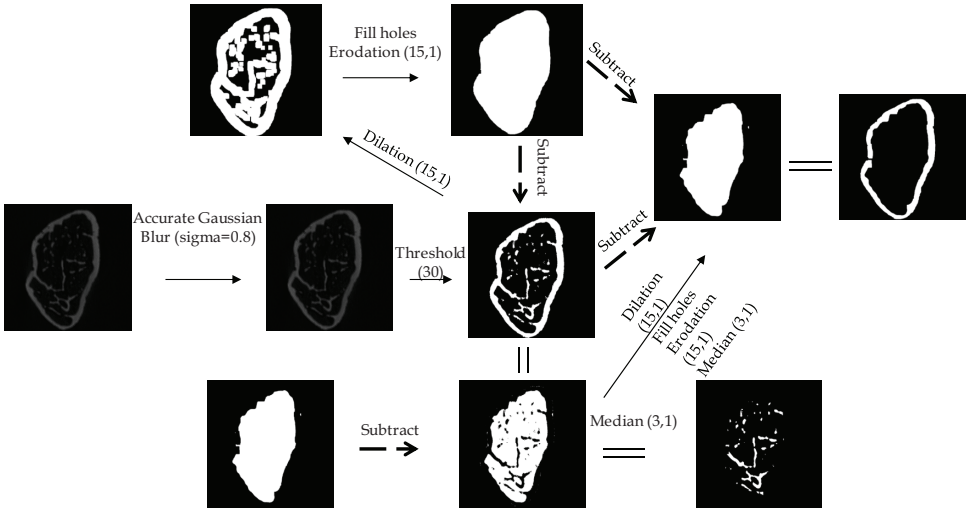


FIGURE 8 The process for segmentation of the cortical and trabecular compartments.

Bone histomorphometry

After the μCT measurement, the L4 vertebra was dehydrated in an increasing series of ethonal, defatted in xylene, and embedded in poly-methylmethacrylate (PMMA). The PMMA blocks were cut longitudinally and the sections used for UV-microscopy of the fluorochromes were adjusted to a thickness of 10 μm and evaluated without counterstaining. The sections for quantitative

histomorphometry analysis were cut into a thickness of 5 μm and stained with the Masson-Golden trichrome method. The specimens were evaluated using light/fluorescent microscopy connected to a computer through a digitizing camera (Olympus, BX-50, Olympus Optical, Tokyo, Japan). For dynamic histomorphometry, the mineralizing apposition rate (μm/day) and osteoid thickness were calculated.

Statistics

Results were expressed as means ± SD. The Shapiro-Wilk test was used to investigate within-group normality for a given parameter of interest. Levene's test was conducted to assess the homogeneity of variances. When normality or equality of variance assumptions was not met, Logarithm transformations were conducted. If these parameters still did not meet normality and equality of variance, nonparametric tests were performed and the Kruskal Wallis Test was used for multiple comparisons with Chi-Square. The Asymp.Sig level was set as $p<0.05$. In the Wilcoxon W test for between-group comparison, the adjusted Asymp.Sig level was set as $p<0.008$. The effects of body mass (with 2 levels: normal and obese), exercise (with 2 levels: sedentary and voluntary wheel running), and their interaction were investigated for each dependent variable using a two-way ANOVA. Trait means of groups were compared and the significance of differences was determined by *post hoc* testing using the Tukey's HSD. A Pearson correlation coefficient was used to determine the relationship between body mass, fat pad, serum factors and the measured bone variables. A p value of < 0.05 was considered statistically significant. All statistical analyses were performed with SPSS 15.0.

5 RESULTS

5.1 Human study (I)

Background information and physical characteristics of twin pairs
The background information and physical characteristics of the twin pairs are given in original publication I. Briefly, the active co-twins had a significantly higher leisure time MET index both at the baseline and follow-up than their inactive counterparts. No significant differences between the active and inactive co-twins in height, weight, BMI, smoking, and alcohol consumption were found at either the baseline or follow-up.

Differences in bone traits between active and inactive co- twins
Among the pooled twin pairs, the active co-twins had larger CSA_{bone} and CSA_{co}, higher $vBMD_{bone,}$ BMC_{tot}, Imax, thicker cortex, and a smaller medullary cavity compared to their inactive co-twins (Table 1). Among the MZ pairs (Table 2), the trend of bone traits was similar to those in the pooled twin pairs, with higher values among the active co-twins. Among the DZ twin pairs, the results were not as systematic as among the MZ pairs: CSA_{bone}, CSA_{m}, and the moments of inertia showed no statistically significant differences between the active and inactive co-twins.

At the distal tibia, the active compared with inactive co-twins of the pooled twin pairs had significantly higher CSI, while the other parameters were similar between the active and inactive co-twins (Table 3). BMC_{tot} and CSI were significantly higher in the active than inactive co-twins among the MZ pairs, while no significant intra-pair differences between the active and inactive co-twins were found among the DZ pairs (Table 4).

With respect to the polar mass distribution (Figure 9A and C), at the tibial shaft both the active and inactive co-twins of both the MZ and DZ pairs had similar BMC in the lateral and medial directions, whereas in the anterior and posterior directions, the active compared with inactive co-twins had significantly higher BMC. At the distal tibia, among the MZ pairs, the active co-

twins had higher BMC in all directions than their inactive counterparts, whereas no significant differences were noticed among the DZ twin pairs.

The radial distribution of bone mineral density around the center of bone mass showed a characteristic sigmoid shape for both the tibial shaft and the distal tibia (Lower panel in Figure 9B and D). Among the MZ twin pairs, the active co-twins had higher bone mineral density from the endosteal to periosteal surface (from 10% to 80%) at both the tibial shaft and the distal tibia than their inactive counterparts. Among the DZ twin pairs, similar results were found at the tibial shaft, but no significant differences were found in radial bone mineral density distribution at the distal tibia.

TABLE 1 BMD and geometry at the tibial shaft in all 16 twin pairs discordant for physical activity. Data are mean ± SD.

Tibia shaft	Inactive	Active	Mean difference (95% CI)	P-value
CSA_{tot} (mm^2)	528 ± 76	533 ± 76	-4 (-24 to 16)	0.64
CSA_{bone} (mm^2)	435 ± 68	453 ± 68	-19 (-35 to -2)	0.050
CSA_{co} (mm^2)	342 ± 58	372 ± 60	-30 (-41 to -19)	<0.001
CSA_{co}/CSA_{tot} ratio	0.65 ± 0.04	0.70 ± 0.04	-0.05 (-0.07 to-0.04)	<0.001
CSA_m (mm^2)	94 ± 20	80 ± 15	14 (3 to 25)	0.014
Th_c (mm)	4.6 ± 0.7	5.3 ± 0.7	-0.7 (-0.9 to -0.5)	<0.001
$vBMD_{bone}$ (mg/cm^3)	958 ± 46	994 ± 45	-37 (-59 to -15)	0.003
$vBMD_{co}$ (mg/cm^3)	1090± 33	1104 ± 28	-14 (-27 to 0)	0.049
BMC_{tot} (mg/cm)	417 ± 69	451 ± 71	-34 (-46 to -22)	<0.001
Ipolar (mgxcm)	4986 ± 1469	5360 ± 1611	-381 (-767 to 5)	0.052
Imax (mgxcm)	3429 ± 1038	3798 ± 1263	-369 (-703 to 35)	0.032
Imin (mgxcm)	1552 ± 495	1561 ± 389	-9 (-129 to 111)	0.87

TABLE 2 BMD and geometry at the tibial shaft in 7 MZ and 9 DZ twin pairs discordant for physical activity. Data are mean ± SD.

Tibia shaft	Inactive	Active	Mean difference (95% CI)	P-value
7 MZ pairs				
CSA_{tot} (mm^2)	521 ± 81	542 ± 87	-21 (-56 to 14)	0.18
CSA_{bone} (mm^2)	425 ± 72	458 ± 80	-33 (-61 to -5)	0.063
CSA_{co} (mm^2)	334 ± 65	374 ± 75	-40 (-61 to -19)	0.003
CSA_{co}/CSA_{tot} ratio	0.64 ± 0.05	0.69 ± 0.05	-0.05 (-0.08 to -0.02)	0.006
CSA_m (mm^2)	96 ± 19	84 ± 16	12 (-3 to 27)	0.095
Th_c (mm)	4.5 ± 0.8	5.2 ± 1.0	-0.8 (-1.2 to -0.3)	0.004
$vBMD_{bone}$ (mg/cm^3)	954 ± 53	982 ± 56	-28 (-57 to 1)	0.057
$vBMD_{co}$ (mg/cm^3)	1090 ± 40	1096 ± 35	-6 (-19 to 7)	0.33
BMC_{tot} (mg/cm)	407 ± 79	451 ± 87	-44 (-70 to -18)	0.006
Ipolar (mgxcm)	4877 ± 1563	5596 ± 1805	-717 (-1379 to -55)	0.038
Imax (mgxcm)	3366 ± 1109	4026 ± 1381	-660 (-1199 to -121)	0.024
Imin (mgxcm)	1514 ± 477	1570 ± 463	-56 (-199 to 88)	0.38
9 DZ pairs				
CSA_{tot} (mm^2)	534 ± 76	526 ± 70	9 (-17 to 34)	0.45
CSA_{bone} (mm^2)	442 ± 68	449 ± 61	-7 (-28 to 14)	0.53
CSA_{co} (mm^2)	349 ± 54	371 ± 51	-22 (-35 to -9)	0.005
CSA_{co}/CSA_{tot} ratio	0.65 ± 0.03	0.71 ± 0.02	-0.05 (-0.08 to -0.03)	0.001
CSA_m (mm^2)	92 ± 21	77 ± 14	16 (-3 to 34)	0.085
Th_c (mm)	4.7 ± 0.6	5.3 ± 0.4	-0.6 (-0.8 to -0.4)	<0.001
$vBMD_{bone}$ (mg/cm^3)	961 ± 42	1004 ± 36	-43.1 (-80 to -6)	0.027
$vBMD_{co}$ (mg/cm^3)	1090 ± 29	1110 ± 21	-20 (-45 to 5)	0.078
BMC_{tot} (mg/cm)	424 ± 65	450 ± 60	-26 (-38 to -14)	0.001
Ipolar (mgxcm)	5057 ± 1483	5177 ± 1528	-120 (-620 to 380)	0.60
Imax (mgxcm)	3478 ± 1044	3621 ± 1216	-143 (-598 to 312)	0.49
Imin (mgxcm)	1581 ± 535	1554 ± 351	27 (-182 to 235)	0.78

TABLE 3 BMD and geometry at the distal tibia in all 16 twin pairs discordant for physical activity. Data are mean ± SD.

Distal tibia	Inactive	Active	Mean difference (95% CI)	P-value
CSA_{tot} (mm^2)	1077 ± 232	1072 ± 189	5 (-54 to 64)	0.87
$vBMD_{tot}$ (mg/cm^3)	307 ± 52	325 ± 48	-19 (-38 to 0)	0.051
$vBMD_{trab}$ (mg/cm^3)	230 ± 48	249 ± 36	-19 (-39to 1)	0.065
BMC_{tot} (mg/cm)	327 ± 74	346 ± 64	-19 (-40 to 15)	0.066
CSI (g^2/cm^4)	1.01 ± 0.33	1.14 ± 0.32	-0.12 (-0.23 to -0.01)	0.034

TABLE 4 BMD and geometry at the distal tibia in 7 MZ and 9 DZ twin pairs discordant for physical activity. Data are mean ± SD.

Distal tibia	Inactive	Active	Mean difference (95% CI)	P-value
7 MZ pairs				
CSA_{tot} (mm^2)	1043 ± 203	1095 ± 212	-51 (-104 to 2)	0.055
$vBMD_{tot}$ (mg/cm^3)	293 ± 46	314 ± 37	-21 (-44 to 2)	0.070
$vBMD_{trab}$ (mg/cm^3)	214 ± 48	241 ± 25	-26 (-53 to 0)	0.050
BMC_{tot} (mg/cm)	307 ± 81	343 ± 76	-37 (-69 to -5)	0.031
CSI (g^2/cm^4)	0.92 ± 0.36	1.09 ± 0.33	-0.17 (-0.33 to 0.01)	0.038
9 DZ pairs				
CSA_{tot} (mm^2)	1103 ± 261	1054 ± 181	49 (-48 to 145)	0.28
$vBMD_{tot}$ (mg/cm^3)	317 ± 57	334 ± 55	-17 (-50 to 16)	0.27
$vBMD_{trab}$ (mg/cm^3)	242 ± 47	255 ± 42	-13 (-47 to 21)	0.41
BMC_{tot} (mg/cm)	343 ± 67	348 ± 57	-5 (-34 to 24)	0.68
CSI (g^2/cm^4)	1.09 ± 0.30	1.18 ± 0.32	-0.08 (-0.26 to 0.10)	0.33

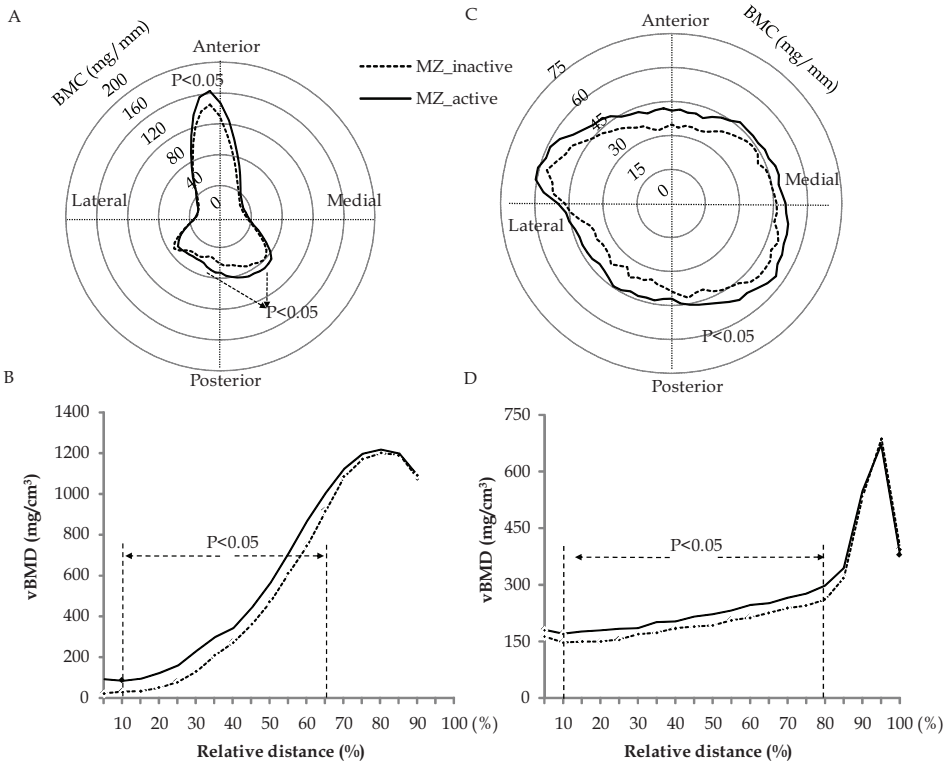


FIGURE 9 Polar mass (BMC, mg/mm) and radial density distribution (vBMD, mg/cm^3) of the tibia shaft (A and B) and the distal tibia (C and D) around the center of mass. The solid line represents the active MZ twin group and the dashed line the inactive MZ twin group. At the midshaft, compared to inactive twins, active twins had significant higher BMC (A) in the anterior-posterior direction, but not in the medial-lateral direction. The active twins also had significantly higher vBMD (B) close to the subcortical area or endocortical region than their inactive co-twins. At the distal tibia, the active co-twins had overall increased BMC (C). The active compared to the inactive co-twins, had significantly higher vBMD between the center of mass and the cortical shell (range: 10% to 80%).

5.2 Animal study (II-IV)

5.2.1 Energy consumption, feed efficiency and body mass

The mice in HF and HFR ingested more calories than the lean mice in C and CR, and voluntary wheel running significantly increased total dietary caloric consumption (Table 5). Under the control rather than high-fat diet, running significantly increased fat, protein, and carbohydrate consumption. Biweekly energy consumption in HF and HFR was significantly higher than that in C and CR. After 4-week intervention, voluntary wheel running significantly increased energy consumption in CR compared to C (Figure 10B).

A significant difference in feed efficiency was found between the mice on the high-fat diet and the mice on the control diet, regardless of access to the running wheel (Figure 10A).

The percentage gain in body mass of the four groups is shown in Figure 10C. After 4 weeks of intervention, significantly higher body mass compared to C and CR was observed in both HF and HFR. From this time point on, the gain in body mass of the mice on the high-fat diet increased continuously, whereas the gain in body mass of the mice on control diet reached the peak value after 12 weeks of intervention. The runners gained slightly less body mass across the whole experiment period, although they ingested more energy, especially in the CR group. Finally, the HF mice gained 18.0 ± 4.0 g compared with 5.3 ± 1.8 g in the C mice, the HFR gained 15.4 ± 3.8 g compared with 5.2 ± 1.4 g in CR.

Consistently with their increased body mass, the mice on the high-fat diet had a heavier liver and epididymal fat pad mass than their counterparts on the control diet.

TABLE 5 Basic data on the mice. Data are mean ± SD (II-IV).

Basic data	Control diet		High-fat diet		ANOVA(P value)		
	C(n=10)	CR(n=10)	HF(n=10)	HFR(n=9)	Diet	Run	D*R
Body mass (g)♯	29.1 (1.0)	28.9 (1.6)	42.0 (4.7)^{ab}	40.2 (5.2)^{ab}			
Liver (mg)†	1057 (136)	1253 (157)	1523 (440)^{a}	1342 (410)^{a}	**<0.05**	0.94	0.09
Epididymal fat (mg)	435 (87)	387 (51)^{a}	1774 (227)^{ab}	1814 (180)^{ab}	**<0.01**	0.94	0.40
Running distance (km)		437 (136)		393 (112)			
Energy consumption							
Total (kcal)	1402 (83)	1513 (76)^{a}	1731 (143)^{ab}	1771 (132)^{ab}	**<0.01**	**<0.05**	0.33
Fat (kcal)♯	56.1 (3.3)	60.5 (3.1)^{a}	1038 (86)^{ab}	1063 (79)^{ab}			
Protein (kcal)♯	259 (15)	280 (14)^{a}	346 (29)^{ab}	354 (26)^{ab}			
Carbohydrate (kcal)♯	781 (46)	843 (43)^{a}	346 (29)^{ab}	354 (26)^{ab}			
GTT and ITT							
AUC_GTT_10w†	1087 (315)	807 (194)^{a}	1448 (432)^{ab}	1561 (559)^{ab}	**<0.01**	0.51	0.13
AUC_GTT_20w	947 (356)	722 (315)^{a}	1527 (216)^{ab}	1575 (466)^{ab}	**<0.01**	0.43	0.23
AUC_ITT_10w	778 (105)	727 (155)	980 (159)^{ab}	862 (242)^{b}	**<0.01**	0.13	0.54
AUC_ITT_20w	812 (183)	767 (169)	992 (190)^{ab}	968 (245)^{b}	**<0.01**	0.59	0.87
$Glu_{10w\text{-}fasting}$ (mmol/L)	9.08 (0.68)	8.29 (0.97)^{a}	9.74 (0.58)^{b}	9.26 (0.92)^{b}	**<0.01**	**<0.05**	0.55
$Glu_{20w\text{-}fasting}$ (mmol/L)	9.26 (1.15)	8.38 (0.92)^{a}	10.31 (1.07)^{ab}	10.28 (0.93)^{ab}	**<0.01**	0.17	0.2

♯Nonparametric tests, Chi-Square Asymp.Sig level was set as $p<0.05$ (Kruskal Wallis Test for multiple comparison). Wilcoxon W test for between-group comparison, adjusted Asymp.Sig level was set as $p<0.008$; $^{a}p<0.05$ *vs.* C; $^{b}p<0.05$ *vs.* CR; $^{c}p<0.05$ *vs.* HF. †Logarithm transformation for normality testing and comparison.

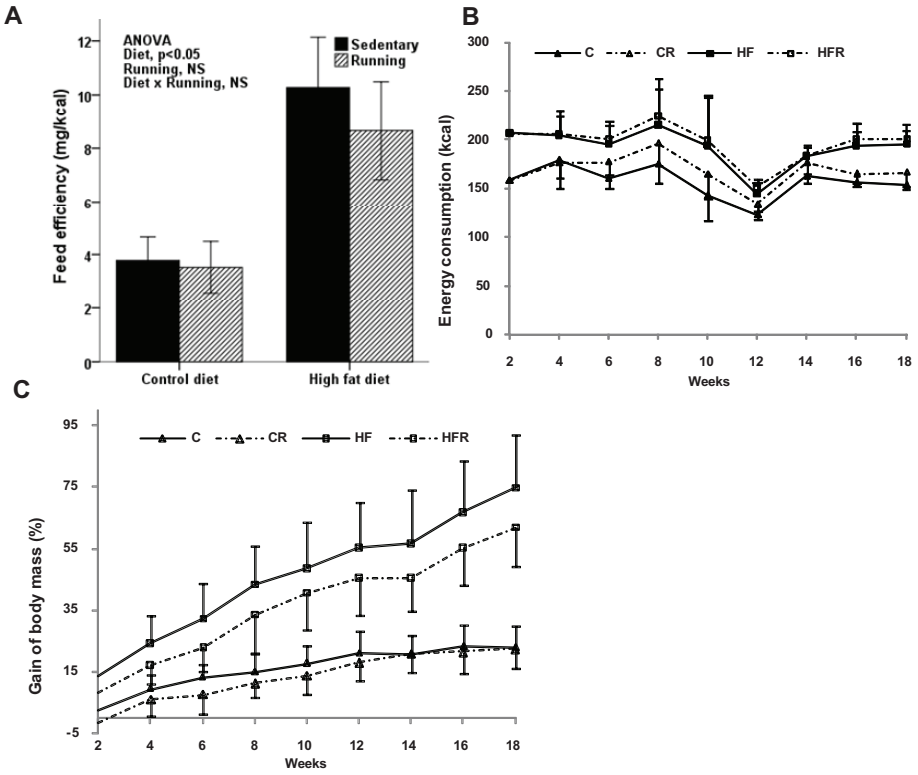


FIGURE 10 Feed efficiency (A) as body mass gained (mg) per unit of energy consumed (kcal) during the 21-week intervention. Biweekly energy consumption (B). The percentage gain in body mass refers to the baseline body mass of the mice in each group during the diet intervention (C) (C = control diet, CR = control diet + voluntary running, HF = High-fat diet, HFR = High-fat diet + voluntary running; n = 9-10 mice/group).

5.2.2 Running distance and maximum running capacity

Wheel-running distance

The daily running distance gradually increased during the first month. However, thereafter at about the 5th week, the mice both in the CR and HFR groups reached their maximum daily running distances, after which the daily running distance decreased gradually (Figure 11A and original publication II). Finally, the average daily running distances were 3.48 ± 1.34 for CR and 3.13 ± 1.13 km for HFR. There were no significant differences between the mice in the CR and HFR groups in either daily running average (Figure 11A) or cumulative running distances (Table 5).

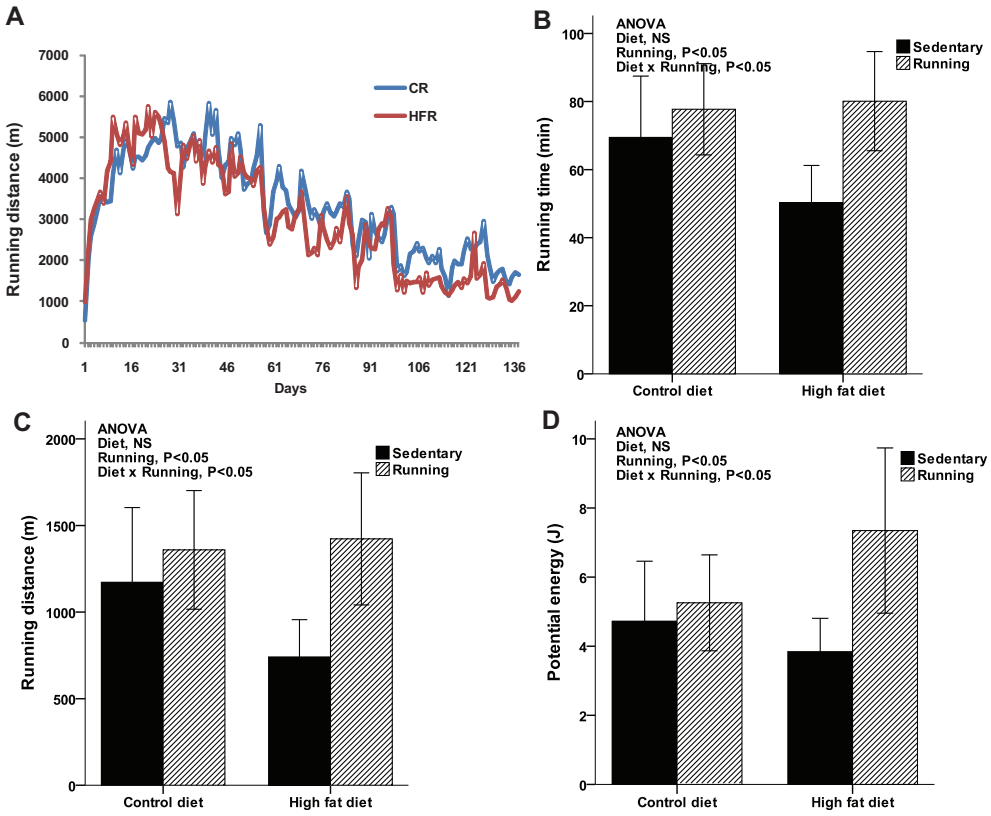


FIGURE 11 Daily voluntary running distance (**A**) during the 21-week intervention. Running time (B), distance (**C**), and potential energy (D) during the forced endurance running test on a motor driven treadmill at wk 16 of the intervention (n = 10 mice/group).

Maximum running capacity

Figure 11B, C, and D shows the results of the exhaustive running tests. Diet and voluntary wheel running training showed a clear interaction for running time,

distance, and potential energy. Voluntary exercise training significantly improved the running capacity of the mice, especially in HFR.

5.2.3 Glucose tolerance and insulin sensitivity

At 10 weeks, two-way ANOVA showed a significant effect of diet on AUC-GTT, suggesting a reduced response of the obese mice to glucose level (Table 5). Similarly, a significant effect of diet was found on AUC-ITT whereby the obese mice had larger AUC-ITT, indicating impaired insulin sensitivity. As expected, at 20 weeks, the obese mice in the HF and HFR groups had a significantly higher fasting glucose level than those at 10 weeks, showing even worse glucose tolerance and insulin sensitivity than those in the C and CR groups. However, voluntary exercise significantly improved this impaired glucose tolerance and insulin sensitivity in CR, but not in HFR. Fasting plasma glucose levels were lower in C and CR than in HF and HFR, but only the CR mice showed significantly reduced fasting plasma glucose level. Altered blood glucose levels after glucose or insulin injection also showed impaired glucose tolerance (Figure 12A and C) and insulin sensitivity (Figure 12B and D) in HF and HFR; the insulin sentivity was also significantly impaired by long-term high-fat feeding.

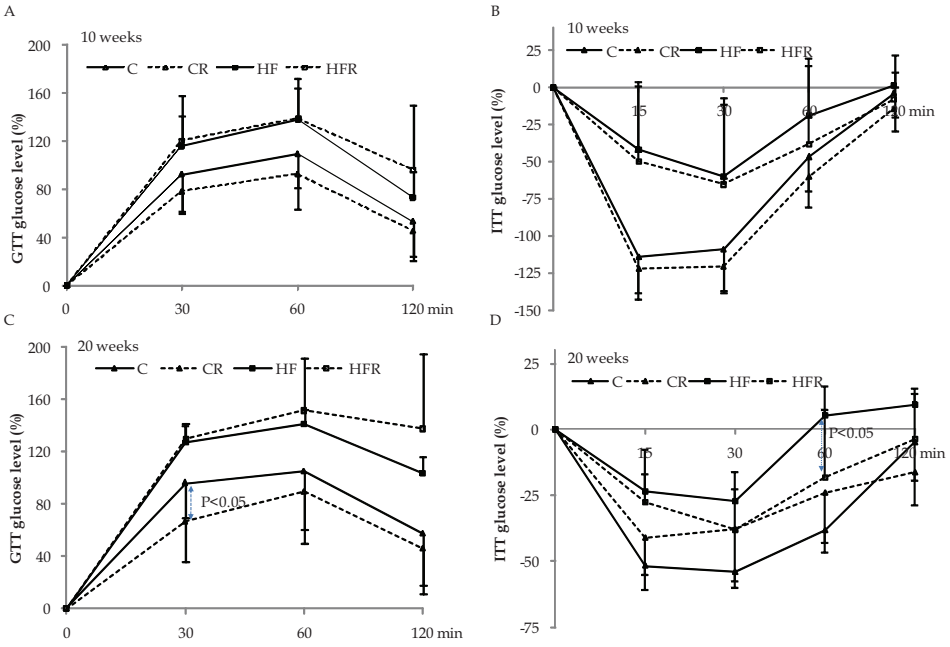


FIGURE 12 Blood glucose level (%) relative to the level measured immediately after glucose injection during the glucose (GTT) and insulin tolerance tests (ITT) after 10 (A and B) and 20 (C and D) weeks of intervention. GTT (2 g/kg, i.p.) in 5-hour fasted C57BL/6J mice and ITT (0.75 U/kg, i.p.) in 2-hour fasting C57BL/6J mice were administered (C = control diet, CR = control diet + voluntary running, HF = High-fat diet, HFR = High-fat diet + voluntary running; n = 9-10 mice/group) (II-IV).

5.2.4 Serum biomarkers

Diet showed a significant main effect on serum insulin, leptin, osteoprotegerin, PAI-1, and resistin level but not on osteocalcin (Figure 13). The mice on the high-fat diet had significantly higher serum insulin, leptin, osteoprotegerin, PAI-1, and resistin levels compared to the mice on the control diet.

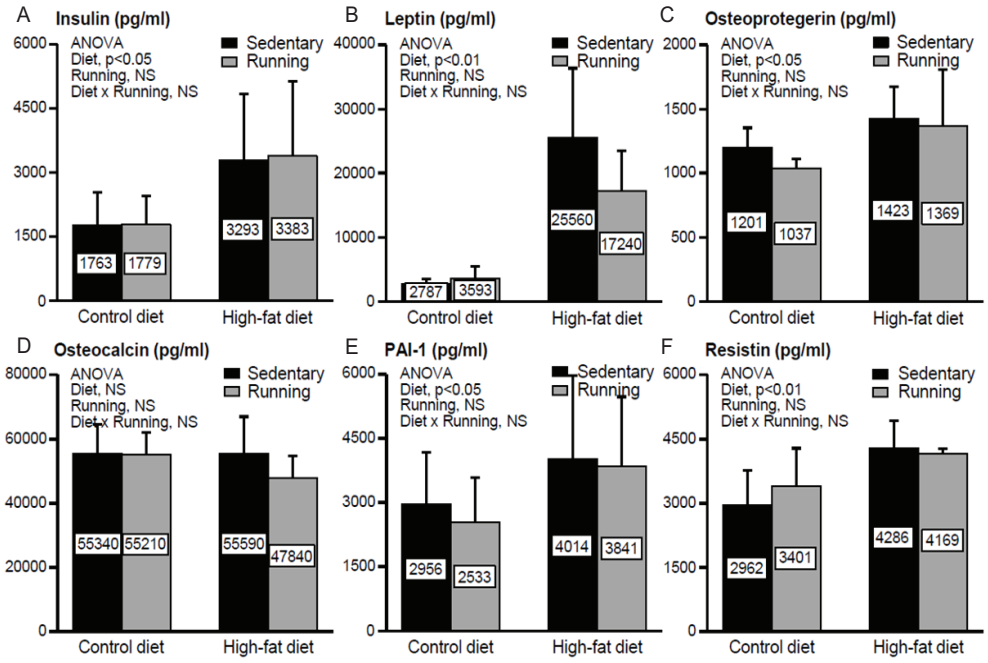


FIGURE 13 Serum factors: insulin (A), leptin (B), osteoprotegerin (C), osteocalcin (D), Plasminogen activator inhibitor-1 (PAI-1: E), and resistin (F). Data presented are means (n=7-10 mice/group, adopted from article III).

5.2.5 Bone properties

pQCT densitometry (II)

The diet- and running-induced effects on the femoral bone traits measured by pQCT are shown in Tables 6 and 7. Two-way ANOVA showed a significant interaction of diet by running on $vBMD_{tot}$ and Th_c in the diaphysis, and $vBMD_{tot}$, BMC_{tot}, CSA_m, CSA_m/CSA_{tot}, and $vBMD_{tra}$ in the metaphysis. Compared to the mice on the control diet, those on the high-fat diet had higher measured bone traits, except for tBMD and CSA_m/CSA_{tot}, in both the diaphysis and metaphysis. The mice on control diet with access to the running wheel had smaller CSI and thinner cortex in the diaphysis and lower $vBMD_{tot}$, BMC_{tot}, moments of inertia, CSI, and larger marrow cavity in the metaphysis. In the mice on the high-fat diet, voluntary wheel running significantly decreased mCSA both in the diaphysis and metaphysis.

The polar mass distribution of bone for the femoral shaft (Fig14 A, B, and C) and distal site (Fig14 D, E, and F) is shown. The mice on the high-fat diet (pooled HF and HFR) had more bone mass in the anterior-medial and posterior-lateral direction in the femoral shaft (Fig14 A) and in the medial and lateral direction in the femoral distal site (Fig14 D) compared to the mice on the control diet (pooled C and CR). Voluntary wheel running (pooled CR and HFR) decreased bone mass in the anterior and medial direction in the shaft and in the medial (Fig14 B) and posterior direction in the femoral distal site (Fig14 E). Among the four groups, HF and HFR as compared with C and CR, had more bone mass, as indicated by Fig14 C and F with similar patterns in Fig14 A and D. Voluntary wheel running decreased bone mass in the femoral shaft in the mice regardless of diet; however, in the distal site, voluntary wheel running under the high-fat diet increased bone mass in the lateral direction and decreased in the medial direction, while under the control diet, voluntary wheel running decreased bone mass in the media-posterior direction and in the lateral-anterior direction.

Figure 15 shows the radial distribution of bone density around the center of bone mass. In the femoral shaft (Figure 15A, B, and C), the mice on the high-fat diet had higher density near the periosteal surface or in the pure cortical area (80% and 85%) (Figure 15A). There were no significant differences between the sedentary and running groups for average bone mineral density from the center of bone mass to the periosteal border (Figure 15B). Similar patterns were also noticed among the four groups. Voluntary wheel running affected bone mineral density in a site-specific manner (Figure 15C). In the metaphysis (Figure 15D, E, and F), in comparison with the mice on the control diet, the mice on the high-fat diet had higher bone density near the endosteal border or the marrow phases (rings 35%-65%) but lower density near the periosteal surface (80%) (Figure 15D). Voluntary wheel running significantly decreased the average bone density near the periosteal surface (65%-85%) (Figure 15E). Voluntary wheel running under the control diet decreased the bone density from the center of mass to the periosteal border (40%-85%), whereas under the high-fat diet, it increased bone density near the center of bone mass, with values ranging from 15% to 45%, and decreased cortical bone density (85%) (Figure 15F).

The measured bone traits, except for $vBMD_{tot}$, CSA_{co}/CSA_{tot}, $CSA_m/tCSA_{tot}$ in the diaphysis, and $vBMD_{tot}$, CSA_m, CSA_m/CSA_{tot}, and $vBMD_{tra}$ in the metaphysis, correlated positively with body mass and fat mass as well as with leptin and OPG. No significant correlations between osteocalcin and the measured bone traits were found. A few of the measured bone traits positively correlated with PAI-1 but negatively with resistin (Table 8 and 9).

TABLE 6 pQCT measurements from slice s5 at the femoral diaphysis dissected from mice after the 21-week intervention. Data are means (SD) (C = control diet, CR = control diet + voluntary running, HF = High-fat diet, HFR = High-fat diet + voluntary running).

Variables	Control diet		High-fat diet		ANOVA (P value)		
	C (n=10)	CR (n=10)	HF (n=10)	HFR (n=9)	Diet	Run	D*R
CSA_{tot} (mm^2)	2.13 (0.12)[c]	2.08 (0.10)[c]	2.34 (0.14)[a,b]	2.34 (0.21)[a,b]	**<0.01**	0.56	0.61
CfB (mm)*	5.30 (0.17)[c]	5.22 (0.14)[c]	5.55 (0.19)[a,b]	5.56 (0.27)[a,b]	**<0.01**	0.61	0.50
$vBMD_{tot}$ (mg/cm^3)	623 (20)	604 (25)	612 (18)	622 (24)	0.57	0.55	**<0.05**
BMC_{tot} (mg/mm)	1.31 (0.05)[c]	1.25 (0.06)[c]	1.41 (0.10)[a,b]	1.44 (0.14)[a,b]	**<0.01**	0.59	0.16
Imax (mgxcm)*	193 (19)[c]	183 (14)[c]	231 (28)[a,b]	237 (44)[a,b]	**<0.01**	0.82	0.40
Imin (mgxcm)*	441 (46)[c]	401 (46)[c]	523 (68)[a,b]	532 (105)[a,b]	**<0.01**	0.52	0.30
Ipolar (mgxcm)	634 (65)[c]	582 (56)[c]	768 (100)[a,b]	769 (145)[a,b]	**<0.01**	0.42	0.40
CSI x 10^3 (g^2/cm^4)*	9.67 (0.43)[b,c]	9.05 (0.60)[a,c]	10.6 (1.0)[a,b]	10.3 (0.7)[a,b]	**<0.01**	0.61	0.49
CSA_m (mm^2)[+]	0.36 (0.06)	0.36 (0.05)	0.44 (0.08)[a,b]	0.39 (0.05)[c]	**<0.01**	0.20	0.20
CSA_m/CSA_{tot} (%)*	16.8 (2.1)	16.9 (1.6)	17.9 (1.4)	16.5 (1.5)	0.51	0.24	0.18
Cortex							
CSA_{co} (mm^2)	1.20 (0.04)[c]	1.14 (0.06)[c]	1.28 (0.09)[a,b]	1.30 (0.11)[a,b]	**<0.01**	0.33	0.11
$vBMD_{co}$ (mg/cm^3)	971 (11)	956 (23)	985 (15)[a,b]	983 (18)[a,b]	**<0.01**	0.12	0.22
BMC_{co} (mg/mm)	1.17 (0.04)	1.09 (0.07)	1.26 (0.10)[a,b]	1.28 (0.13)[a,b]	**<0.01**	0.26	0.11
Th_c (mm)	0.21 (0.01)	0.19 (0.02)[a]	0.21 (0.01)[b]	0.21 (0.02)	**<0.01**	0.30	**<0.01**
CSA_{co}/CSA_{tot} (%)*	67.9 (2.1)	66.2 (2.3)	67.5 (2.1)	66.7 (2.2)	0.88	0.09	0.52

[a]$p<0.05$ *vs.* C; [b]$p<0.05$ *vs.* CR; [c]$p<0.05$ *vs.* HF. *Unpublished, [+]Logarithm transformation for normality and comparison.

TABLE 7 pQCT measurements from slice s3 at the femoral metaphysis dissected from mice after the 21-week intervention. Data are means (SD) (C = control diet, CR = control diet + voluntary running, HF = High-fat diet, HFR =High-fat diet + voluntary running).

Variables	Control diet		High-fat diet		ANOVA (P value)		
	C (n=10)	CR (n=10)	HF (n=10)	HFR (n=9)	Diet	Run	D*R
CSA_{tot} (mm^2)	3.54 (0.17)	3.40 (0.16)	3.85 (0.22)[a,b]	3.81 (0.34)[a,b]	**<0.01**	0.23	0.50
CfB (mm)*	7.25 (0.16)	7.05 (0.22)	7.53 (0.29)[a,b]	7.51 (0.29)[a,b]	**<0.01**	0.16	0.28
$vBMD_{tot}$ (mg/cm^3)	435 (10)	408 (36)[a]	418 (11)[a]	425 (18)	0.87	0.14	**<0.05**
BMC_{tot} (mg/mm)	1.54 (0.09)	1.39 (0.13)[a]	1.61 (0.10)[b]	1.62 (0.16)	**<0.01**	0.07	**<0.05**
Imax (mgxcm)	324 (35)	285 (33)[a,c]	380 (53)[a,b]	371 (75)[a,b]	**<0.01**	0.17	0.36
Imin (mgxcm)	955 (95)[c]	850 (101)[a,c]	1067 (119)[a,b]	1055 (163)[a,b]	**<0.01**	0.15	0.26
Ipolar (mgxcm)	1276 (119)	1123 (125)[a]	1448 (167)b	1425 (234)[a,b]	**<0.01**	0.11	0.23
CSI x 10^3 (g^2/cm^4)*	7.12 (0.45)	6.32 (0.61)[a]	7.22 (0.50)[b]	6.62 (0.59)[b]	**<0.05**	**<0.05**	0.12
CSA_m (mm^2)[+]	0.25 (0.15)	0.33 (0.18)[a]	0.35 (0.09)[a]	0.20 (0.06)[b,c]	0.94	0.37	**<0.01**
CSA_m/CSA_{tot} (%)*	5.87 (1.19)[c]	8.17 (2.68)[a]	9.16 (2.34)[b]	5.44 (1.79)[b,c]	0.68	0.3	**<0.01**
Trabeculae							
CSA_{tra} (mm^2)	2.34 (0.14)	2.42 (0.21)	2.67 (0.17)[a,b]	2.70 (0.30)[a,b]	**<0.01**	0.45	0.75
BMC_{tra} (mg/mm)	0.67 (0.06)	0.70 (0.05)	0.75 (0.05)[a,b]	0.82 (0.10)[a,b]	**<0.01**	**<0.05**	0.43
$vBMD_{tra}$ (mg/cm^3)	285 (17)	289 (13)	283 (10)	302 (8)[a,c]	0.15	**<0.01**	**<0.05**

[a]$p<0.05$ *vs.* C; [b]$p<0.05$ *vs.* CR; [c]$p<0.05$ *vs.* HF. *unpublished, [+]Logarithm transformation for normality and comparison.

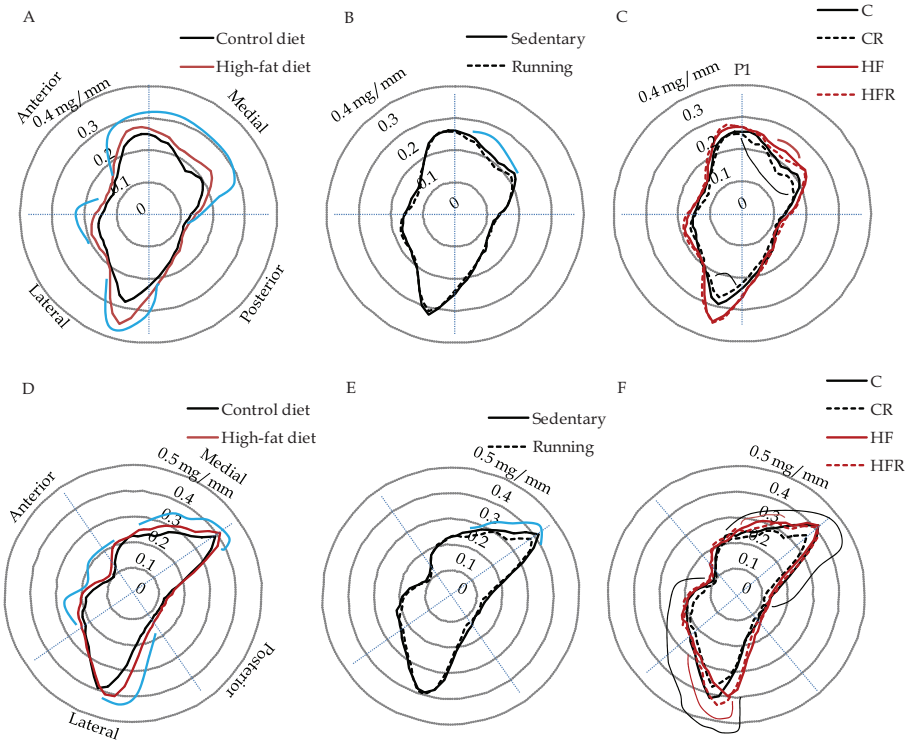


FIGURE 14 Polar mass distribution (BMC, mg/mm) from slice s5 at the femoral shaft (A, B, and C) and from slice s3 at the distal metaphysis (D, E, and F). The blue curve in A, B, D, and E indicates significant differences between groups. The red and black curves in E and F represent the significant differences between HF and HFR, and between C and CR, respectively. The control diet group includes both C and CR; the high-fat group includes both HF and HFR. A and D show the diet effects, B and E show the running effects, C and F show the differences among the four groups (Sedentary = C +HF, Running = CR + HFR).

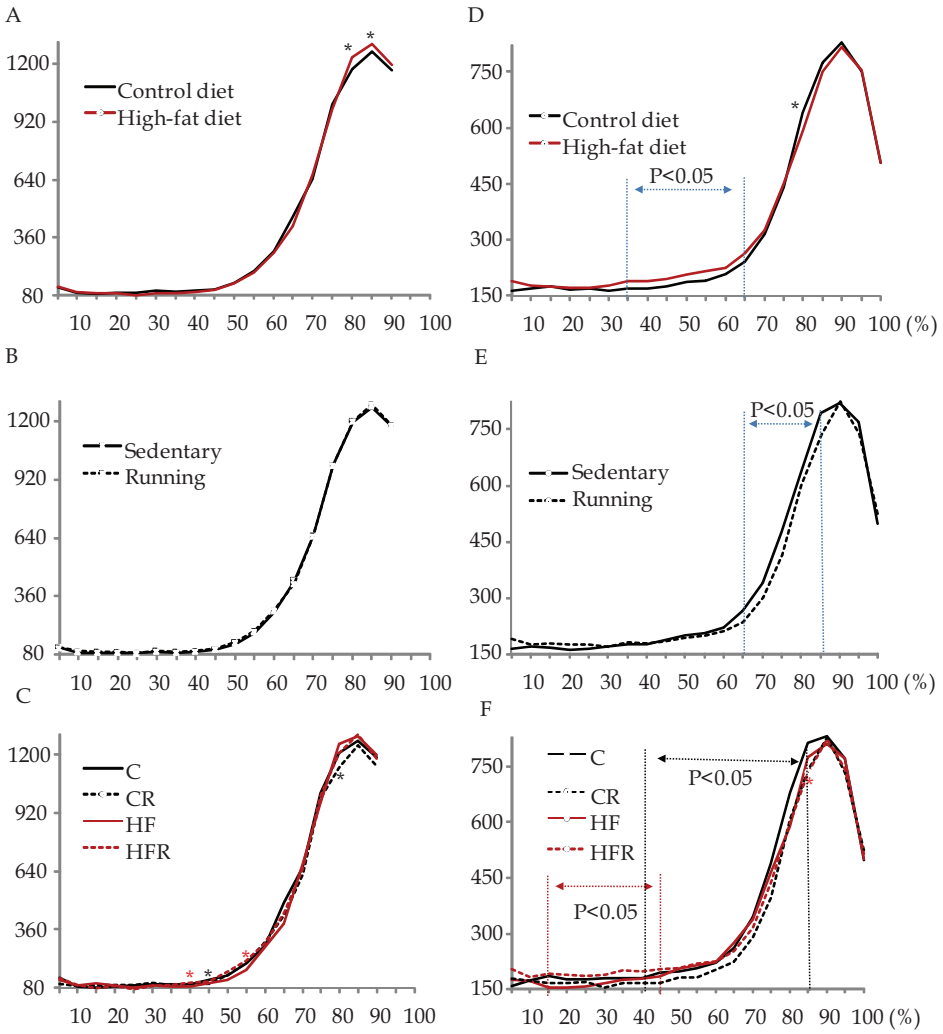


FIGURE 15 Radial density distribution (mg/cm³) from slice 5 at the femoral shaft (A, B, and C) and from slice 3 at the femoral distal metaphysis (D, E, and F) (*p<0.05). The black star (*) and p<0.05 in A, D, and E represents the significant differences between the control diet and high-fat diet group. In C and F, the black star (*) represents the significant differences between C and CR, and the red star (*) represents the significant differences between HF and HFR. The control diet group includes both C and CR; the high-fat group includes both HF and HFR. In Figure 15C and F the color represents the corresponding groups (Sedentary = C +HF, Running = CR + HFR).

TABLE 8 Pearson correlation coefficients between body mass, epididymal fat pad, serum factors, and bone traits from slice s5 in the femoral diaphysis. Results are r-values.

Variables	Body mass n=40	Fat pad n=38	OPG n=38	Leptin n=38	Osteocalcin n=38	PAI_1 n=37	Resistin n=34
CSA_{tot}	0.842**	0.699**	0.508**	0.620**	-0.207	0.402*	-0.352*
CfB	0.824**	0.697**	0.439**	0.642**	-0.246	0.357*	-0.313
$vBMD_{tot}$	-0.007	0.045	-0.172	-0.057	-0.148	0.137	0.029
BMC_{tot}	0.808**	0.701**	0.410*	0.582**	-0.262	0.285	-0.366*
Imin	0.855**	0.707**	0.548**	0.591**	-0.214	0.400*	-0.424*
Imax	0.832**	0.695**	0.419**	0.650**	-0.232	0.356*	-0.298
Ipolar	0.850**	0.709**	0.463**	0.642**	-0.23	0.374*	-0.337
CSI x 10^3	0.751**	0.650**	0.349*	0.624**	-0.206	0.286	-0.192
Cortex							
CSA_{co}	0.793**	0.685**	0.377*	0.574**	-0.256	0.233	-0.352*
$vBMD_{co}$	0.633**	0.556**	0.324	0.497**	-0.175	0.309	-0.305
BMC_{co}	0.795**	0.686**	0.380*	0.582**	-0.25	0.258	-0.355*
Th_c	0.439**	0.436**	0.099	0.298	-0.256	-0.061	-0.255
CSA_{co}/CSA_{tot}	0.092	0.025	-0.068	0.149	0.01	-0.056	0.127
CSA_m	0.564**	0.402*	0.518**	0.402*	-0.13	0.345*	-0.268
CSA_m/CSA_{tot}	0.145	0.051	0.316	0.123	0.014	0.237	-0.006

*p<0.05; **p<0.05.

TABLE 9 Pearson correlation coefficients between body mass, epididymal fat pad, serum factors, and bone traits from slice s3 in the femoral metaphysis. Results are r-values.

Variables	Body mass n=40	Fat pad n=38	OPG n=38	Leptin n=38	Osteocalcin n=38	PAI_1 n=37	Resistin n=34
Metaphysis							
CSA_{tot}	0.798**	0.664**	0.509**	0.588**	-0.212	0.25	-0.356*
CfB	0.796**	0.687**	0.501**	0.570**	-0.214	0.286	-0.383*
$vBMD_{tot}$	-0.13	-0.143	-0.3	-0.126	0.155	-0.207	0.187
BMC_{tot}	0.676**	0.551**	0.330*	0.490**	-0.137	0.135	-0.318
Imin	0.750**	0.631**	0.414*	0.559**	-0.18	0.155	-0.303
Imax	0.747**	0.601**	0.438**	0.544**	-0.224	0.269	-0.339
Ipolar	0.764**	0.622**	0.437**	0.562**	-0.212	0.243	-0.329
CSI x 10^3	0.399*	0.319	0.165	0.306	-0.1	-0.004	-0.11
CSA_m	0.135	0.187	0.12	0.179	-0.023	-0.014	0.175
CSA_m/CSA_{tot}	-0.033	0.043	0.013	0.064	0.015	-0.05	0.256
Trabeculae							
CSA_{tra}	0.796**	0.694**	0.556**	0.573**	-0.281	0.294	-0.456**
$vBMD_{tra}$	0.127	0.179	0.005	0.05	0.002	0.308	-0.466**
BMC_{tra}	0.722**	0.647**	0.482**	0.497**	-0.241	0.069	0.024

*p<0.05; **p<0.05.

MicroCT measurements (III-IV)

In the distal femur (Slice 4) (Table 10), diet showed significant main effects on BV, BS, BS/BV, Tb.Th and Tb.Sp, and had marginal effects on SMI and Tb.N. The mice on the high-fat diet had larger trabecular BV and BS, thicker trabeculae, and a lower bone surface/volume ratio but higher SMI than the mice on the control diet. Voluntary wheel running also showed significant main effects on SMI and Tb.Pf, and especially under the high-fat diet decreased these two parameters (III).

In the 1-mm ROI from the distal femur, the obese mice had significantly larger tissue volume and total bone volume. Consistently, larger trabecular BV and BS, higher BV/TV and trabecular thickness, and lower BS/BV were found in the obese mice. SMI was elevated in obese mice as well. Voluntary wheel running showed significant effects on SMI. Under the high-fat diet, running significantly decreased SMI. Compared to the lean mice, the obese mice had slightly higher BMD in the trabecular compartment of the metaphysis but not in the cortical shell. In all the groups, higher density voxels localized in the anterior direction in response to physical activity or increased body mass were found (IV).

Two-way ANOVA showed a significant main effect of diet on vertebral BV, BS, Tb.Th, Tb.Sp, and DA. Compared to the mice on the control diet, the mice on the high-fat diet had significantly larger BV and BS, thicker trabeculae and smaller trabecular separation but a higher degree of anisotropy (increased with aging) and slightly higher connectivity density, implied by decreased Euler.N and increased Conn.D (Table 10). Voluntary wheel running had a marginal main effect on Euler.N ($p = 0.069$) and Conn.D ($p = 0.064$), showing that the runners had slightly decreased trabecular connectivity when compared with their counterparts. A marginal interaction of diet and voluntary wheel running on Tb.N ($p = 0.063$) was also found, where voluntary wheel running under the control diet decreased Tb.N and increased under the high-fat diet.

Figure 16 shows the representative 3D trabecular structure of the distal metaphysis of the femur and the core of the L4 vertebra. In the femoral metaphysis, a plate-like trabecular structure in the obese mice with the access to wheel running was found.

TABLE 10 Trabecular parameters measured by µCT from the femur and L4 vertebra dissected after the 21-week intervention. Values are mean (SD) (C = control diet, CR = control diet + voluntary running, HF = High-fat diet, HFR = High-fat diet + voluntary running).

MicroCT	Control diet		High fat diet		ANOVA (P value)		
	C (n=10)	CR (n=10)	HF (n=9)	HFR (n=9)	Diet	Run	D*R
Distal femur: trabecular (corresponding to Slice 4 from pQCT) (III)							
Conn.D (mm^{-3})	337 (129)	367 (105)	466 (138)	415 (88)	**<0.05**	0.81	0.34
BV (10^{-1} mm^3)	0.09 (0.02)	0.10 (0.04)	0.11 (0.03)	0.15 (0.03)[ab]	**<0.01**	0.069	0.33
BS (mm^2)	1.59 (0.24)	1.70 (0.52)	1.85 (0.39)	2.23 (0.37)[ab]	**<0.05**	0.11	0.36
BS/BV (mm^{-1})	171 (6)	167 (10)	160 (10)	154 (11)[ab]	**<0.05**	0.14	0.74
Tb.Pf (mm^{-1})	72.8 (3.4)	69.2 (6.1)	72.1 (7.0)	63.9 (6.2)[ac]	0.17	**<0.01**	0.26
SMI	2.60 (0.07)	2.54 (0.11)	2.74 (0.12)[b]	2.53 (0.11)[c]	0.089	**<0.01**	0.061
Tb.Th (µm)	23.7 (1.2)	23.7 (1.2)	26.1 (0.9)[ab]	25.3 (1.7)[ab]	**<0.01**	0.45	0.39
Tb.N (mm^{-1})	0.29 (0.02)	0.33 (0.11)	0.34 (0.08)	0.43 (0.09)[ab]	0.068	0.16	0.29
Tb.Sp (µm)	429 (4)	428 (9)	418 (10)	414 (13)[ab]	**<0.01**	0.35	0.63
DA	3.52 (1.49)	3.72 (1.15)	4.08 (1.52)	3.73 (1.36)	0.58	0.88	0.59
Distal femur: trabecular (1 mm ROI) (IV)							
Conn.D (mm^{-3})	568 (113)	570 (181)	620 (163)	508 (133)	0.93	0.3	0.28
BVx10 (mm^3)	0.32 (0.04)	0.32 (0.09)	0.37 (0.08)	0.39 (0.05)[a,b]	**<0.05**	0.86	0.63
BS (mm^2)	4.68 (0.54)	4.53 (1.11)	5.06 (1.04)	5.37 (0.62)	0.06	0.79	0.46
BS/BV(mm^{-1})	146 (7)	146 (11)	137 (8)[a,b]	139 (5)[a,b]	**<0.05**	0.63	0.64
Tb.Pf (mm^{-1})	56.9 (4.5)	56.6 (5.7)	57.8 (4.0)	54.8 (4.0)	0.79	0.31	0.41
SMI	2.40 (0.11)	2.38 (0.10)	2.58 (0.11)[a,b]	2.41 (0.15)[c]	**<0.01**	**<0.05**	0.08
Tb.Th (µm)	26.6 (1.1)	26.3 (1.7)	29.5 (2.0)[a,b]	27.7 (1.3)[c]	**<0.01**	0.06	0.15
Tb.N (mm^{-1})	0.47 (0.06)	0.46 (0.12)	0.48 (0.11)	0.53 (0.07)	0.19	0.57	0.33
Tb.Sp (µm)	542 (32)	538 (31)	520 (33)	536 (42)	0.29	0.61	0.41
DA	2.33 (0.38)	2.65 (0.54)	2.32 (0.28)	2.44 (0.29)	0.43	0.11	0.46
Vertebral body: trabecular (unpublished)							
Conn.D (mm-3)	292 (83)	230 (102)[c]	350 (103)[b]	290 (116)	0.07	0.07	0.98
BVx10 (mm3)	1.40 (0.20)	1.34 (0.19)	1.50 (0.12)[b]	1.54 (0.14)[b]	**<0.01**	0.88	0.38
BS (mm2)	7.62 (1.19)	7.49 (0.51)	7.80 (0.40)	8.21 (0.33)[b]	**<0.05**	0.55	0.23
BS/BV (mm-1)	54.4 (2.4)	55.1 (4.0)	52.1 (2.6)	53.6 (3.7)	0.08	0.31	0.71
Tb.Pf (mm-1)	8.13 (6.01)	9.38 (3.85)	7.92 (3.27)	8.59 (4.19)	0.72	0.5	0.84
SMI	1.00 (0.28)	1.16 (0.24)	1.18 (0.23)	1.18 (0.28)	0.22	0.33	0.37
Tb.Th (µm)	62.3 (3.7)	62.2 (3.0)[c]	66.3 (3.3)[a,b]	64.0 (5.1)	**<0.05**	0.35	0.37
Tb.N (mm-1)	2.79 (0.39)	2.67 (0.20)	2.69 (0.17)	2.86 (0.12)	0.57	0.74	0.06
Tb.Sp (µm)	207 (16)	208 (10)	199 (11)	192 (7)[a,b]	**<0.01**	0.36	0.23
DA	1.94 (0.26)	2.26 (0.35)[a]	2.38 (0.27)[a]	2.40 (0.36)[a]	**<0.01**	0.1	0.14

[a]$p<0.05$ *vs.* C; [b]$p<0.05$ *vs.* CR; [c]$p<0.05$ *vs.* HF.

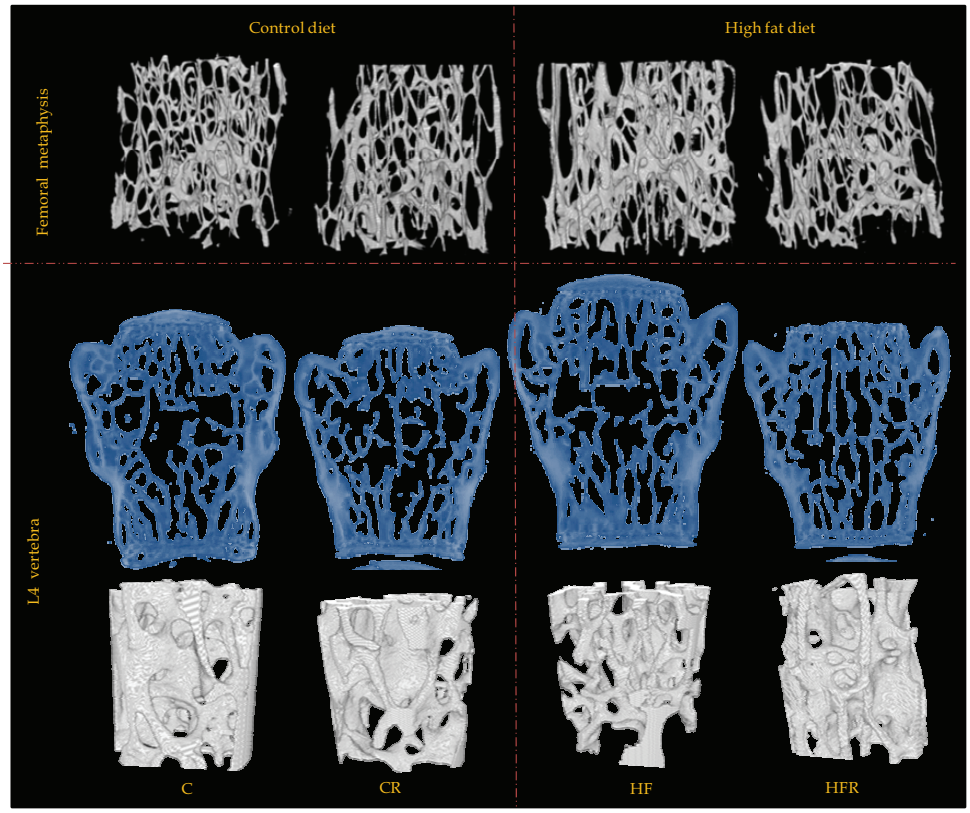


FIGURE 16 Representative 3D structure of the distal metaphysis of the femur and the L4 vertebra. The rod-like trabeculae are dominant in the distal metaphysis of the femur, while the plate-like trabeculae are dominant in the vertebra. For the distal metaphysis, compared to the mice on the control diet, the larger and thicker trabeculae were found in the mice on the high-fat diet. The mice on the control diet had a smoother trabecular surface in the L4 vertebra than the mice on the high-fat diet. The rough trabecular surface in the vertebra was more evident in the mice on the high-fat diet without running (the blue images represnt saggital sections of L4 and the white images reprent the cylinder core in the middle of L4).

Biomechanical testing

No significant interactions of diet by running on the mechanical properties of these three bones were found. In the femoral neck, the high-fat diet had a significant main effect by increasing peak load and elastic modulus (Slope), whereas voluntary running decreased the peak load (II). No significant effects of running, diet, and their combination on the mechanical properties of L4 were found (Table 11). In the tibia shaft, significantly higher energy at the peak load was found in the mice on the high-fat diet than in the mice on the control diet.

TABLE 11 Biomechanical properties of the femoral neck, vertebral body, and tibia. Values are means (SD). (C = control diet, CR = control diet + voluntary running, HF = High-fat diet, HFR = High-fat diet + voluntary running)

Biomechanics	Control diet		High fat diet		ANOVA (P value)		
	C (n=10)	CR (n=10)	HF (n=9)	HFR (n=9)	Diet	Run	D*R
Femur neck							
Femur length (mm)	15.2 (0.2)	15.0 (0.2)	15.0 (0.3)	15.0 (0.2)	0.06	0.14	0.10
Peak load (N)	23.9 (3.2)	22.2 (2.7)	28.1 (4.4)[a,b]	24.8 (4.5)[c]	**<0.01**	**<0.05**	0.51
$Displace_{peak\ load}$ (mm)	0.21 (0.04)	0.20 (0.05)	0.21 (0.04)	0.22 (0.04)	0.54	0.16	0.12
$Energy_{peak\ load}$ (J)	4.43 (0.63)	3.33 (0.95)	4.83 (1.62)	4.51 (1.85)	0.08	0.11	0.38
Fracture load (N)	19.8 (5.0)	17.7 (5.1)	23.8 (5.5)	19.8 (5.7)	0.09	0.09	0.58
$Displace_{fracture\ load}$ (mm)	0.37 (0.07)	0.35 (0.13)	0.36 (0.12)	0.37 (0.09)	0.83	0.78	0.59
$Energy_{fracture\ load}$ (J)	5.62 (1.35)	4.72 (1.97)	6.59 (3.71)	5.98 (2.41)	0.169	0.349	0.85
Slope (N/mm)	31.6 (8.9)	35.6 (8.3)	40.8 (8.5)[a]	38.7 (5.8)[a]	**<0.05**	0.721	0.24
*Vertebral body**							
Height (mm)	2.90 (0.06)	2.89 (0.16)	3.06 (0.12)	2.98 (0.14)	**<0.01**	0.41	0.31
Width (mm)	2.28 (0.05)	2.27 (0.07)	2.28 (0.08)	2.32 (0.06)	0.25	0.44	0.32
Peak load (N)	18.2 (4.6)	17.7 (3.3)	18.1 (6.0)	17.9 (53.8)	0.98	0.81	0.93
$Displace_{peak\ load}$ (mm)	0.57 (0.23)	0.68 (0.24)	0.50 (0.24)	0.52 (0.33)	0.08	0.48	0.56
$Energy_{peak\ load}$ (J)	6.05 (3.08)	7.72 (3.25)	6.41 (5.14)	6.22 (6.60)	0.19	0.62	0.39
Fracture load (N)	10.9 (3.2)	10.4 (2.1)	10.9 (3.7)	12.9 (5.2)	0.29	0.53	0.31
$Displace_{fracture\ load}$ (mm)	0.99 (0.45)	1.11 (0.42)	0.89 (0.40)	0.81 (0.36)	0.11	0.84	0.47
$Energy_{fracture\ load}$ (J)	11.5 (6.6)	13.5 (5.9)	11.7 (8.1)	10.2 (6.6)	0.48	0.83	0.47
Slope (N/mm)	66.3 (19.4)	72.1 (19)	73.8 (27.7)	67.7 (19.6)	0.83	0.99	0.39
*Tibia shaft**							
Tibia length (mm)	18.3 (0.3)	18.3 (0.3)	18.1 (0.2)	18.1 (0.3)	0.38	0.75	0.42
Peak load (N)	16.4 (1.9)	15.2 (2.0)	16.6 (2.3)	17.5 (2.6)	0.11	0.79	0.17
$Displace_{peak\ load}$ (mm)	0.05 (0.01)	0.04 (0.01)	0.05 (0.01)	0.05 (0.00)	0.09	0.23	0.58
$Energy_{peak\ load}$ (J)	1.90 (0.39)	1.64 (0.23)	2.01 (0.34)	2.08 (0.41)	**<0.05**	0.44	0.18
Fracture load (N)	6.28 (1.15)	5.85 (1.25)	7.33 (1.71)	6.31 (1.97)	0.16	0.18	0.58
$Displace_{fracture\ load}$ (mm)	1.18 (0.33)	0.94 (0.49)	1.27 (0.40)	1.19 (0.34)	0.22	0.24	0.55
$Energy_{fracture\ load}$ (J)	9.57 (3.07)	6.82 (4.09)	10.2 (3.1)	9.70 (3.13)	0.15	0.18	0.34
Slope (N/mm)	148 (16)	142 (19)	140 (20)	155 (23)	0.71	0.5	0.14

[a]$p<0.05$ *vs.* C; [b]$p<0.05$ *vs.* CR; [c]$p<0.05$ *vs.* HF. *unpublished.

Histomorphometry (Unpublished)

No significant effects of diet, voluntary wheel running, and their combination on osteoid thickness and bone formation rate were found. However, the mice

on the high-fat diet had a slightly thicker osteoid compared to the mice on the control diet (Figures 17 and 18). Figure 18 shows the adipocyte distribution in the bone marrow. In the mice on the high-fat diet, the adipocytes were evenly distributed over the marrow cavity, while in the mice on the control diet they were more localized in certain areas. Figure 19 shows the bone formation labeling.

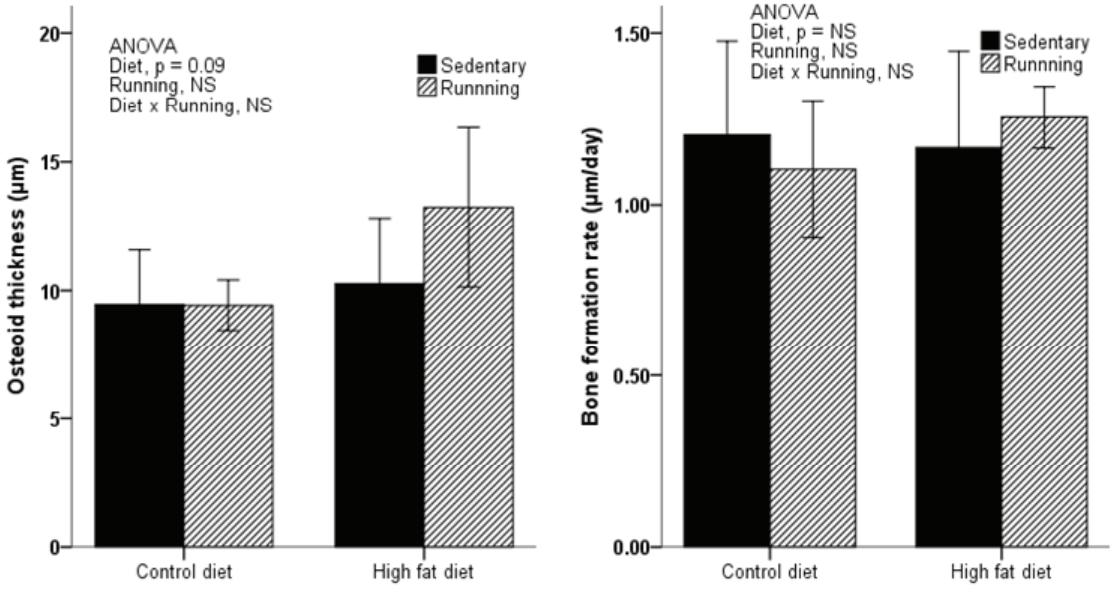


FIGURE 17 Osteoid thickness and bone formation rate of the L4 vertebra dissected after the 21-week intervention. Diet shows a marginal effect on osteoid thickness.

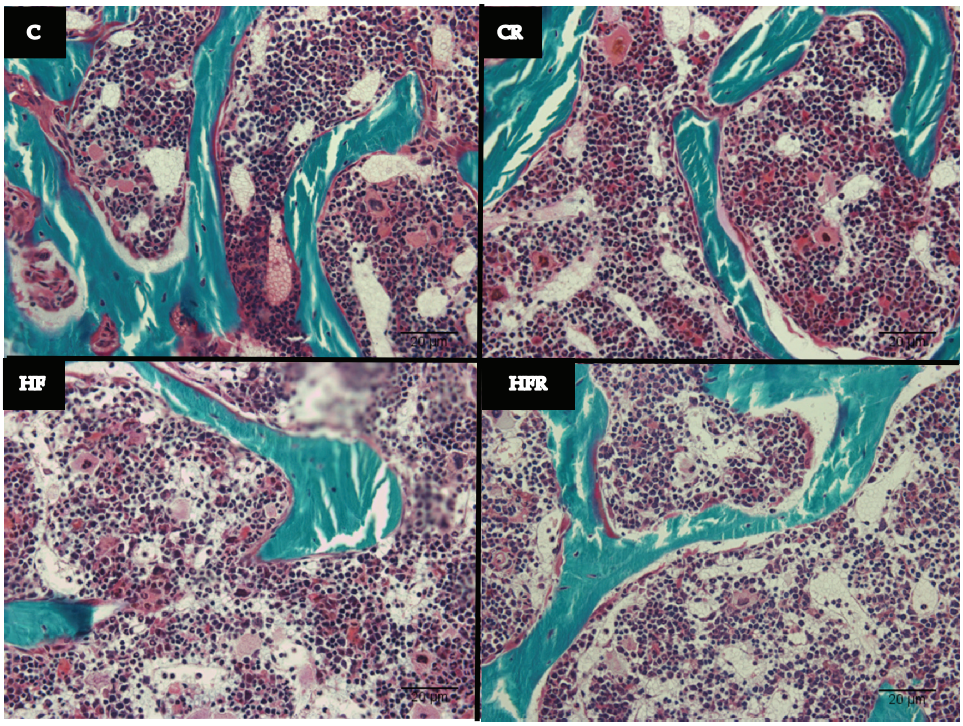


FIGURE 18 Masson-Goldner trichrome staining of bone section from the L4 verterbra dissected after the 21-week intervention. Blue-stained represents mineralized bone; red-stained bone surfaces represent the new-formed osteoid. Within the marrow cavity, adipocytes present a foam-like structure with light-red-stained networks. Adipose tissue is distributed more collectively in C and CR compared to HF and HFR (C = control diet, CR = control diet + voluntary running, HF = High-fat diet, HFR = High-fat diet + voluntary running).

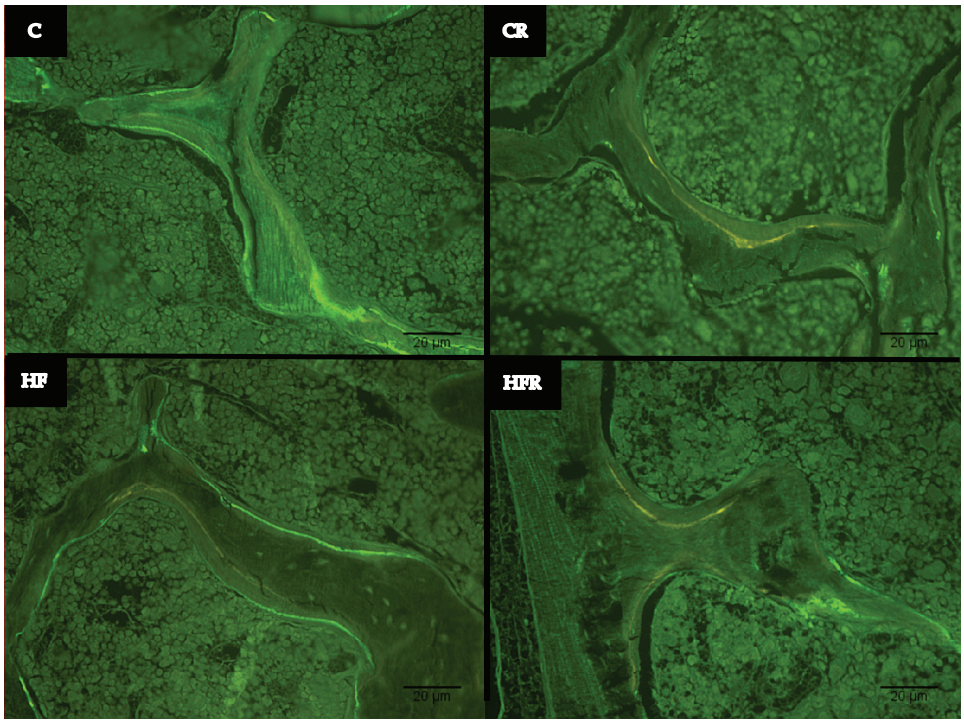


FIGURE 19 Fluorescent labeling of bone sections from the L4 vertebra dissected after the 21-week intervention. Light green color represents calcein incorporated into bone and yellow represents tetracycline labeling. The labeled line can be seen in all groups (C = control diet, CR = control diet + voluntary running, HF = High-fat diet, HFR = High-fat diet + voluntary running).

6 DISCUSSION

6.1 Long-term leisure time physical activity and bone

The results based on pooled twin pairs, comprising MZ and DZ pairs, suggest that LTPA during adulthood is associated with stronger bones. The results from the MZ twin pairs confirmed that, independent of hereditary factors, LTPA during adulthood seems to improve bone strength (resistance to fractures) in a site-specific manner, i.e., by increasing bone mass through markedly increasing diaphyseal cortical cross-sectional area and thickness as well as metaphyseal trabecular BMD, and by changing anatomical bone mass distribution. These changes led to increased bending strength along the anterior-posterior direction in the tibial shaft and increased compressive strength in the distal tibia. This suggests that cortical and trabecular bone at the tibia may display different adaptation patterns in response to long-term physical activity.

As mentioned earlier, physical activity, such as both weight-bearing and non weight-bearing exercise, has been shown to be associated with increased DXA-based BMC and aBMD as well as HAS-derived strength indices. However, these DXA-based studies failed to provide information on the adaptation of cortical and trabecular bone to physical activity. In the present study, the application of pQCT allows the responses of the diaphyseal cortical and the metaphyseal trabecular bone to physical activity to be evaluated separately. Consistent with previous studies, the active co-twins, compared to their inactive counterparts, also showed higher BMC after controlling for genetic factors, suggesting that LTPA during adulthood has the potential to increase or at least maintain bone mass.

Here, a smaller marrow cavity and thicker cortex but no markedly elevated cortical BMD were observed in the tibial diaphysis among the active co-twins compared to their inactive counterparts, as was also found in one previous study (Haapasalo et al. 2000). In fact, the biggest difference between the athletes and referents was observed in long bone geometry. Bone hypertrophy of the shaft both in the tibia and in the radius has previously been

observed in former athletes (Jones et al. 1977; Chang et al. 2009; Deriaz et al. 2010; Ducher et al. 2010; Rantalainen et al. 2010). Similarly, associations of physical activity with increased cortical cross-sectional area and cortical thickness at the tibial shaft have also been reported in long-term recreational gymnasts (Sone et al. 2006), a school-based physical activity in young boys (Macdonald et al. 2009), and a population based study (Lorentzon et al. 2005). A thicker metacarpal cortical index in the dominant hand of middle-aged teachers and dentists has also been observed (Vehmas et al. 2005). Similarly, even short-term training (Pang et al. 2006; Pang and Lau 2010) for people with chronic stroke and postmenopausal women (Uusi-Rasi et al. 2003) led to cortical thickening at the tibia. In the present study, with thicker cortex and narrower medullary cavity, bone cross-sectional area increased but the total cross-sectional area or circumference of the tibia remained unchanged. A similar result was reported in a previous study on young male athletes (Sone et al. 2006), indicating no effects of physical activity on periosteal deposition, but instead delayed or retarded endocortical resorption. These findings emphasize the positive effect of physical activity on bending strength at the tibial shaft.

However, the adaptation of cortical bone mineral density to physical activity is not parallel with the geometrical or structural adaptation of cortical bone. Increasing the bone's resistance to torsion, bending, or compression can be achieved by modifying bone form and mass, but not necessarily by increasing bone density. This is especially the case in the long bone shaft; a unilateral physical activity, such as tennis, provides the most reliable evidence. In tennis, the dominant arm in long-term players during childhood (Bass et al. 2002) or young adulthood (Ashizawa et al. 1999; Haapasalo et al. 2000; Ducher et al. 2004; Ducher et al. 2005) showed dramatically increased cortical bone area and narrowed medullary cavity but with only slight or non-existant improvement in volumetric density. Findings similar to those of the present study have also been reported in the femurs of Olympic fencers (Chang et al. 2009) and in the tibia of runners (Smock et al. 2009) and of growing girls participating in a 9-month trial (Heinonen et al. 2000). In a population-based study, the amount of physical activity was associated with increased cortical thickness, periosteal circumference, and trabecular vBMD, but not with cortical vBMD of the long bones in young men (Lorentzon et al. 2005). In contrast, resistance and agility training have been shown to increase cortical bone mineral density in 75- to 85-year-old women, who are commonly osteoporotic individuals (Liu-Ambrose et al. 2004). Studies have also reported less cortical BMD in the dominant leg compared to the non-dominant leg in athletes mostly involved in basketball, volleyball and soccer (Sone et al. 2006). These discrepancies are possibly due to the threshold used to separate the cortical and trabecular components in the pQCT images and to the experiment design. Other cofactors, such as maturity stages, age of the participants, types of physical activity, and gender also contribute to the inconsistent results on the effects of physical activity on cortical bone mineral density. The present finding that the adaptation of bone in the tibial shaft is primarily due to alterations in

bone size and geometry rather than the bone density is in agreement with the previous notion that bone is the product of a compromise between stiffness *vs*. lightness and rigidity *vs.* toughness.

The response of the long bone metaphysis to physical activity is more consistent with the previous literature; the present finding that physical activity was a combination of increased trabecular BMD and cross-sectional area, leading to an increase in the compressive strength index, indicated adaptation of the metaphysis to its primary locomotive loading. Previous studies have shown increased BMC and trabecular BMD in the distal radius of young adults (Kontulainen et al. 2002) and middle-aged tennis players (Nara-Ashizawa et al. 2002), and in the proximal tibia of male long-distance runners (Deriaz et al. 2010) as well as in the distal femur of Olympic fencers (Chang et al. 2009). Consistent with our results, a previous randomized controlled trial suggested that high-impact training in postmenopausal women may retard trabecular bone loss or maintain distal tibial trabecular BMD (Uusi-Rasi et al. 2003). The same group further demonstrated that long-term recreational gymnastics can retard functional decline and bone loss (Uusi-Rasi et al. 2006). Recent studies have further demonstrated beneficial effects of a mechanical loading intervention on distal tibial bone density for patients with spinal cord injury (Dudley-Javoroski and Shields 2008a). A few recent studies have also reported that physical activity was associated with increased trabecular number and volume fraction in the tibia (Modlesky et al. 2008; Nilsson et al. 2010; McKay et al. 2011). These studies suggest that adaptation of the metaphysis is not only manifested by its size and density, but also by its micro-structure.

The amount and regional distribution of bone mineral around the centre of mass ultimately determine overall bone strength. Thus, the ultimate purpose of physical activity is to optimize bone strength through modifying bone mass and bone geometrical structures as well as bone mineral regional distribution. This optimization will be achieved by modeling, mainly during growth, and by remodeling during adulthood or old age. The present study showed that active co-twins had more bone mass in the anterior-posterior direction but rather similar bone mass in the medial-lateral direction compared to their inactive co-twins in the tibial diaphysis, which is in accordance with the findings of a recent study (Bailey et al. 2010), suggesting non-uniform and direction-specific geometric adaptation of the tibial diaphysis to mechanical loading. However, other studies have also shown a thickened cortex in the medial-lateral direction in young boys involved in physical activity (Macdonald et al. 2008a; Macdonald et al. 2009) and in male adult athletes (Shaw and Stock 2009). These differences could be explained by different types of exercise or loading patterns. The stresses experienced by the midshaft of most long bones are primarily the result of bending, produced by axial forces transmitted about the bone's longitudinal curvature (Biewener 1991). In the present study, most of the activities studied have similar loading patterns to running or walking, which generally represent unidirectional locomotor patterns on the principle planes of deformation in the anterior-posterior direction corresponding to the Imax axis. As an adaptive

response of bone to loading, bone mass will be relocated or added in the anterior-posterior direction, but not in the medial-lateral direction (Lanynon 1992; Leppanen et al. 2010). In the tibial metaphysis, bone mass distribution in response to physical activity is more uniform, as manifested in the overall increased bone mass in the active co-twins, together with the changes in Imax and Imin, indicating dramatically increased compressive strength (Figure 9).

Previous studies have shown that the density of the cortical matrix in the long bone shaft is not uniform; instead it varies across the cortex showing a sigmoid pattern from the endosteal to periosteal surface (Bousson et al. 2000; Bousson et al. 2001). This variation in density is largely attributed to regional differences in porosity (Feik et al. 1997; Nyssen-Behets et al. 1997) and degree of mineralization as well as osteon density (Bergot et al. 2009), which are controlled by bone modeling/remodeling associated with mechanical/non mechanical stimuli during growth (Rauch et al. 2007) or aging (Zebaze et al. 2010). One recent study reported that, with aging, 47% of total bone loss in the distal radius is attributed to bone remodeling within the cortex adjacent to the marrow (Zebaze et al. 2010). The present study clearly demonstrated the beneficial effects of physical activity on bone, showing that in the female twin pairs the active co-twins had higher bone mineral density from the center of bone mass to near the periosteal surface, in both the tibial diaphysis and metaphysis, than their inactive counterparts (unpublished).

Alterations in bone structural and material properties will lead to mechanical adaptation. In the present study, increased Imax in the anterior-posterior direction and Ipolar as well as increased compressive strength index in the tibial metaphysis were observed, indicating increased resistance to bending and torsional load in the tibial diaphysis, and an increased compressive strength in the tibial metaphysis. Similar results have also been reported in runners (Greene et al. 2006; Smock et al. 2009), field hockey players (Shaw and Stock 2009), long-term jumpers (Liu et al. 2003), and world-class female athletes participating in swimming and gymnastics (Liang et al. 2005). Adolescent girl athletes habitually exposed to high or low training loads displayed a higher bone strength index (BSI, the product of volumetric cBMD and cross-sectional moment of inertia within the ROI) at the distal tibia than controls (Greene et al. 2005). In population-based studies, physical activity has been shown to be positively associated with BSI at the metaphysis of the distal femur and tibia and with SSI at the diaphysis of the same sites (Farr et al. 2010a), and with BSI and polar SSI at both the middle and distal tibia and radius in older men (Cousins et al. 2010).

The current results therefore indicate that LTPA could have an important clinical value in the prevention of osteoporosis and reduction of bone fracture risk through optimizing bone mass, size, and geometry as well as mineral distribution in both cortical and trabecular bone.

6.2 Voluntary wheel running and bone

The effects of voluntary wheel running on bone properties were more complicated. In the lean mice, running decreased compressive strength and cortical thickness in the diaphysis and all of the metaphyseal trait values with enlarged CSA_m, increased the degree of anisotropy in both the distal femur and the vertebral body, and decreased the preak load of the femoral neck. In the diet-induced obese mice, voluntary wheel running increased bone mass and narrowed the bone marrow cavity both in the diaphysis and the metaphysis of the femur, improved the 3D microstructure of the femoral metaphysis, and shortened the height of the vertebral body but increased peak load of the femoral neck. Voluntary wheel running increased BMD_{tra} regardless of diet. In accordance with the present results on the obese mice, previous animal studies have reported protective effects of different types of exercise on trabecular BMD (Iwamoto et al. 2005; Weiler et al. 2006; Hamrick et al. 2006; Ocarino et al. 2007; Nagasawa et al. 2008; Plochocki et al. 2008; Welch et al. 2008). Earlier studies have shown that voluntary wheel running for 6 weeks in 6-week-old male Sprague-Dawley rats significantly increased femoral and tibial lengths, weights, and volumes, BMC and BMD at all the other sites studied apart from the distal femur, cross-sectional areas and polar moment of inertia at the femoral mid-shaft (Newhall et al. 1991).

Voluntary wheel running for 4,5 months in 13-month-old female F344 rats increased tibial diaphyseal cortical bone area, cortical thickness, cortical BMC, periosteal perimeter, and SSI (Banu et al. 1999; Kalu et al. 2000) as well as cancellous bone area in the vertebra, proximal tibial metaphysis, and distal femoral metaphysis and cortical bone area and BMC in the vertebra, proximal tibial metaphysis, distal femoral metaphysis and femoral neck (Banu et al. 2001). Further studies have reported in male mice that genetically selected high capacity runners have increased hindlimb bone diameter, mass, and strength with enlarged femoral condyles and reduced directional asymmetry of hindlimb bones (Garland and Freeman 2005; Kelly et al. 2006; Middleton et al. 2008). Recent studies also reported that voluntary wheel running significantly reduced bone turnover and prevented cancellous bone loss due to the preservation of trabecular number in the distal femur in androgen receptor knockout mice (Ophoff et al. 2009) and compensated for bone volume loss in the tibia of rats with cancellous bone loss induced by a high phosphorus and/or low calcium-diet (Begot et al. 2010). In contrast, voluntary wheel running provided no clear osteoprotection in growing male and female rats against goserelin acetate-induced bone degeneration (Hydock et al. 2008). In summary, the effects of voluntary wheel running on bone remain inconsistent and the results between different experiments less comparable.

The majority of the previous studies have focused on either cortical or trabecular bone mass or strength, while only a few studies have reported on micro-structural alteration under voluntary wheel running. The present study

showed that voluntary exercise in obese mice significantly increased trabecular surface area, decreased the trabecular pattern factor and structure model index as well as trabecular thickness in the femoral distal metaphysis, but showed no effects on the spine. Ealier, no reports have been published on the effects of voluntary wheel running on bone in obese mice.

Somewhat unexpectedly, voluntary wheel running in the lean mice was negatively associated with bone traits in the diaphysis and the metaphysis of the femur and bone mechanical properties in the femoral neck and tibial shaft, but positively with trabecular degree of anisotropy both in the spine and the distal femoral metaphysis, even after adjusting for body mass (unpublished). Previous studies found reduced bone mass and strength in mice tibia after 3 weeks of weight-bearing running during growth (Wallace et al. 2007). A recent study reported reduced mid-tibial volumetric BMD and strength in 23-week-old female C57BL/6J mice after 1 month of voluntary wheel running (Warren et al. 2007). This discrepancy might be explained by activated modeling or remodeling of bone during growth under continuous mechanical stimulation (Kyung et al. 2009; Luu et al. 2009). The present study showed a slightly decreased OPG level in plasma in the lean mice with access to the running wheel, indicating decreased bone formation; however, whether this was caused by increased bone remodeling or osteoclast activity can not be confirmed. Retarded longitudinal bone growth and increased bone loss in young rats under strenuous training (Bourrin et al. 1994) has been reported earlier, showing decreased tibial length, bone mineral density in the proximal tibia, bone volume and number of trabeculae in the spongiosa and Tb.Th, but increased Tb.N in the epiphysis. Histomorphetric analysis further elucidated that the bone loss was mostly due to impaired osteoblastic activity as osteoid thickness was reduced but without changes in either osteoclast number or osteoid surfaces. Retarded longitudinal bone growth was also manifested in another study by a shortened growth plate and proliferation zone as well as increased degree of mineralization in immature rats with voluntary access to a running wheel (Niehoff et al. 2004).

Further studies found a time-dependent effect of voluntary climbing exercise on bone, i.e., that intermittent climbing increased trabecular bone volume and reduced bone resorption, initially partially due to down-regulated marrow osteoclastogenic cells and up-regulated osteogenic cells initially, while further exercise desensitized these parameters (Mori et al. 2003). The present results also showed that the runners had a relatively larger trabecular area - active metabolic region of bone compared to their counterparts, although trabecular microstructural parameters were not significantly influenced. Therefore, the adaptation of bone to physical activity in animals, as in human subjects, is more complex and influenced by multiple factors. It is possible that the negative associations observed between physical activity and bone properties are due to the relative caloric restriction. Energy restriction in 34-day-old female Sprague-Dawley rats was shown to decrease femoral and tibial BMC after 14 weeks of voluntary wheel running (Dimarco et al. 2007). In the

present study, although the lean mice with voluntary access to a running wheel consumed more calories than their sedentary counterparts, their daily running distance, which was comparable with that of the obese runners, reflected restricted energy consumption from another perspective. Another possible explanation may be an exercise-induced weight loss accompanied by a generalized bone loss because of reduced direct mechanical strain on the skeleton. Modest weight loss induced by exercise training caused a reduction in BMD in postmenopausal women participating in a 6-month weigt loss program (Chao et al. 2000; Gozansky et al. 2005). In contrast, other studies have reported that exercise-induced weight loss did not accompany bone loss (Pritchard et al. 1996; Stewart et al. 2005; Villareal et al. 2006). Therefore, whether exercise-induced body weight loss accompanies bone loss remains controversial.

In general, in C57BL/6J mice (Halloran et al. 2002), from the age of 6 weeks trabecular volume and number continuously decrease while trabecular thickness and spacing in the tibia increase. Before 24 weeks, the skeleton has matured (Somerville et al. 2004). In the present study, voluntary wheel running maintained for 21 weeks since the age of 7 weeks, was performed across the rapidly growing period. Although numerous data indicate that during the growing period, the effect of physical activity on bone is imposed more efficiently, the protective or detrimental effects of exercises on bone remain a complicated and controversial issue (Daly 2007). Human studies have shown that retired athletes maintaining moderate exercise were able to inhibit bone loss or at least maintain bone mass, indicating a positive effect of exercise. On the basis of the present study, the adaptation of bone to long-term voluntary exercise is site-specific, in both the regional skeleton and in the individual bone, and is also component-specific, i.e., that trabecular and cortical bone show different patterns in response to physical activity.

6.3 Diet-induced obesity and bone

In order to understand the adaptation of bone to physical activity and body weight, the separate and combined effects of diet-induced obesity (static loading) and voluntary wheel running (dynamic loading) on the peripheral and axial skeleton were further investigated in growing mice. The present results showed that diet-induced obese mice had larger bones and more abundant and thicker trabecular bone both in the distal femur and in the spine, a stronger diaphysis and metaphysis, and a stronger tibial diaphysis, compared to their lean controls.

In line with the present study, an earlier study reported improved femoral biomechanics in mature male diet-induced obese rats (Brahmabhatt et al. 1998), while a recent study showed that despite an increase in bone quantity, yield and peak load, reductions occurred in size-independent mechanical properties such as strength, bending stiffness, and fracture toughness in the femur of diet-induced obese C57BL/6 mice, indicating reduced bone quality (Ionova-Martin

et al. 2010). Diet-induced obese mice have consistently been shown to have reduced trabecular bone mass in the tibia (Cao et al. 2009) and alveolar bone (Amar et al. 2007), and reduced aBMD in different skeleton sites (Halade et al. 2010). In another recent study, the lumbar spine in diet-induced obese mice showed decreased trabecular bone volume and aBMD as well as an increased structure model index, indicating a change in bone micro-architecture from a plate- to rod-like appearance in response to increased body mass or obesity itself (Patsch et al. 2011). However, in the present study, in the distal femur, despite increased bone volume and thicker trabeculae, the structure model index of the obese mice also showed higher values. The diet-induced obese mice showed increased trabecular bone volume, thicker trabeculae, and smaller trabecular separation, but a higher degree of anisotropy in the lumbar spine. The present study further demonstrated that in the spine, these microstructural variations between obese and lean mice were not reflected across the mechanical properties of the whole bone. These discrepancies indicate the complexity of animal studies and that the compromised comparability between different studies is due to variations in animal models and study designs as well as different measuring techniques.

However, despite the discrepancies in these studies, it is clear that obesity can affect bone properties either through direct mechanical loading or through indirect biological signals. In the present study, an enlarged marrow cavity and increased total bone cross sectional area (circumference), resulting in larger and stronger bone, was indicated by a higher density-weighted moment of inertia (bending strength), both of the femoral diaphysis and metaphysis, and CSI of the femoral diaphysis as well as increased trabecular cross sectional area, vBMD, BV, BS, Tb.Th of the distal femur. After adjusting for body mass (unpublished), the differences in most of the bone traits between the obese and lean mice were diminished. This suggests an adaptation to increased body mass manifested by an increase in bone mass and strength.

The increased secretion of bone-protecting factors from adipose tissue would be the second contributor to the increase in bone mass and strength. Recently, adipose tissue has been recognized not just as a passive tissue for the storage of excess energy as triglycerides, but also as an active endocrine organ secreting a variety of biologically active molecules, for example, leptin (Hamrick and Ferrari 2008), resistin (Thommesen et al. 2006) and adiponectin (Gomez-Ambrosi et al. 2008). Increased serum leptin level, regarded as a predictor of body mass accrual in different species, has been frequently reported (Dourmashkin et al. 2005; Leibowitz et al. 2006; Gallou-Kabani et al. 2007). It has been shown that leptin inhibits bone formation through the central nervous system (Ducy et al. 2000) while that peripheral leptin is positively associated with bone formation and negatively with bone resorption, leading to increased bone mass (Hamrick et al. 2005). Consistent with earlier reports, the obese mice in the present study showed higher serum leptin levels. A positive correlation between serum leptin level and pQCT-measured bone traits, except for BMD_{tot} in both the diaphyseal and metaphyseal regions, was also noticed.

This suggests a positive association between serum leptin level and femoral geometry and strength. However, previous studies on the exact effects of leptin levels on bone remain inconsistent (Cock and Auwerx 2003; Hamrick and Ferrari 2008). Resistin is a controversial inflammatory-related factor (Koerner et al. 2005), which increases bone remodelling activity by acting both on osteoclast and osteoblast activity (Thommesen et al. 2006). The higher plasma leptin and resistin levels in obese mice suggest a positive effect of these factors on bone remodeling. However, their effects on bone mass and strength were the opposite: bone mass and strength was positively associated with plasma leptin levels but negatively with resistin levels. Increased bone mass with increased body mass independent of leptin was also reported by a recent study (Iwaniec et al. 2009). The mechanism of the interaction between bone metabolism and resistin remains unclear.

Despite the positive effects of obesity on bone, the development of obesity is associated with chronic inflammatory status, coinciding with significantly increased macrophage infiltration in adipose tissue and the expression of inflammatory cytokines, such as tumor necrosis factor-α, interleukin-6, monocyte chemotactic protein-1, and PAI-1 (Weisberg et al. 2003). All of these inflammatory reactions are considered to be responsible for the majority of the obesity-related syndromes. Not surprisingly, this inflammatory status also influences bone metabolism through altering the microenvironment surrounding bone cells. Over-expression of PAI-1 increases bone strength and mineralization in an age- and gender- specific manner (Nordstrom et al. 2007). Here, a higher PAI-1 level was found in the obese mice, and significantly correlated with trabecular thickness, suggesting that PAI-1 may have positive effect on bone (IV). In addition to these altered adipokins and inflammatory factors, a higher level of osteoprotegerin, coinciding with increased osteoid thickness but a similar bone formation rate, was observed in the obese mice, indicating that obesity caused a delay in the mineralization process.

6.4 Adaptation of bone to mechanical loading

The primary function of the skeleton is to provide mechanical support for body mass and locomotion. In the present study, in agreement with a previous notion, when adjusted for body mass, the most elevated bone parameters in the obese mice diminished in comparison to their lean controls (unpublished). Adaptation of bone in response to mechanical loading is not uniform, and increased or decreased parameters measured by current techniques do not necessarily mean better or worse bone. The cellular mechanism by which physical activity affects bone mass and structural properties was not the focus of our study. The frequency, duration, type, rate and distribution of mechanical loading have been investigated in relation to bone cell function. Mechanical loading has been shown to have direct effects on the osteogenic and osteoclastogenic potential of bone marrow mesenchymal stem cells in mice (Mori et al. 2003) and rats, (Song

et al. 2007; Nagasawa et al. 2008) and also on osteoblast cell proliferation (Singh et al. 2007). Furthermore, the balance between bone formation and resorption is determined by osteoblasts and osteoclasts, which are the main participants during modelling and remodelling. The relative stability of cortical bone mineral density may be partly due to delayed intracortical bone remodelling in response to mechanical loading (Terrier et al. 2005). In order to adapt to mechanical strain variables, the skeleton should optimally change its size or, alternatively, its trabecular density by increasing bone strength with minimal increases in bone weight. Animal studies provide us with valuable data, suggesting that mechanical loading or physical activity increases cortical thickness (Hubal et al. 2005; Castillo et al. 2006; Zhang et al. 2006) and trabecular cross-sectional area and density (Warner et al. 2006). In line with these previous animal experiments, the present results, along with the previous human studies (Nikander et al. 2006; Vainionpää et al. 2007) suggest that physical activity has different effects on cortical and trabecular bone.

6.5 Strengths and limitations of this study

The main strength of the present study on human subjects was that it was possible to adjust the results for childhood environment (all twin pairs) and genes (MZ pairs) and that there was long-term (32-year) discordance in LTPA habits between the two co-twins. The main limitation of this study was its cross-sectional nature with respect to the measured bone parameters, although we know that MZ co-twins usually have very similar physical activity habits during childhood. Therefore, it was not possible to provide further evidence on whether the higher parameters found in the active co-twins compared to their inactive counterparts are the results of retarded bone loss or increased bone gain during adulthood in response to physical activity. In addition, the relatively small sample size affects the generalizability of our results. Intra-pair differences in bone traits in response to mechanical loading among the discordant DZ pairs showed effects of both physical activities and genes on bone.

The main strength of the animal study was that it was possible to separately evaluate the effects of diet-induced obesity and voluntary wheel running on the macro- and micro- structural and material properties of cortical and trabecular bone by using pQCT and microCT respectively. The present study demonstrated that voluntary wheel running in the diet-induced obese mice was able to improve bone strength and 3-D micro-architecture. The other strength was that both sedentary controls and voluntary wheel running controls were used; this provides the possibility of distinguishing the positive or negative effects of these interventions on bone. This study has three main limitations. First, the small sample sizes in each group weakened statistical power of the comparisons between most of the variables, especially with respect to within-group differences. Marginally significant separate and

combined effects of voluntary wheel running and diet-induced obesity on bone were observed. A larger sample size would have assisted in the interpretation of the results. Second, to ensure an apparent identical environment, voluntary running wheels would need to be placed in each cage, while only allowing the mice in the exercise group to access running freely. Finally, it was not possible to separate the effects of diet-induced obesity from that of diet on bone. Therefore, the effects of diet-induced obesity on bone contain effects both of diet and body mass, and possibly aslo their interaction with voluntary exercise.

6.6 Future perspectives

The present study on human subjects demonstrates that the adaptation of bone to long-term leisure time physical activity is manifested by optimizing material (mineral mass), structurel (cortex and trabeculae), and geometry, also in individual bones in a site-specific manner. However, owing to the segmentation method or threshold used in the pQCT image analysis, it remains controversial whether cortical bone mineral density is also involved in this adaptation process in response to mechanical stimulus. It is not clear whether the dramatically increased bone mass in the anterior-posterior direction at the tibia shaft is caused by the apposition of the new cortex or by purely increased mineral density of the existing cortex. A regional density map would be helpful in seeking to understand the mechanisms of bone adaptation to long-term leisure time physical activity.

The animal study provides valuable data for further investigation of the biological mechanisms behind the adaptation of bone to mechanical loading. Some evidence on these mechanisms has been reported. However, so far, the situation of "more questions than answers" has not been reversed in the last 100 years. Invevitably, this is also the case in the present study. During recent years, osteoporosis and obesity have become more and more prevalent. The similarities and discrepancies in their etiologies have received increasing research attention. It is well known that most of the bone marrow cavity has been occupied by adipose tissue in old people but not necessarily accompanied by obesity or osteoporosis as currently diagnosed. The present experiment showed that adipose tissue in the marrow cavity presented a dispersive pattern in the obese mice but a collective distribution in the lean mice. However, "weaker bone" in the obese mice was not found; instead, the obese mice had stronger bone and better trabecular bone indicators. It is possible that obesity has detrimental effects on size-independent mechanical properties; this possibly calls for further study.

7 MAIN FINDINGS AND CONCLUSIONS

The main results and conclusions of the present study can be summarized as follows:

1. Long-term leisure time physical activity, independent of genes, can improve bone quality by increasing cortical thickness, bending and torsion rigidity at the tibial shaft, and trabecular mineral density and compressive strength at the distal tibia in a site-specific manner.
2. Diet-induced obesity in growing mice was associated with larger bone circumference and cross-sectional area and higher density-weight maximal, minimal, and polar moment of inertia in the femur, with stronger femoral neck and tibial shaft, but not with mechanical properties of the spine. It was also associated with increased trabecular bone volume, bone surface, BS/BV ratio, thickness in both the distal femur and the spine, with smaller trabecular spacing in the spine, and with an increased degree of anisotropy in the spine and increased structure model index in the distal femur, indicating a shift from plate-like to rod-like trabeculae.
3. Voluntary wheel running was associated with increased trabecular BMD and a decreased structure model index in the metaphysis implying a shift from rod-like to plate-like trabeculae in response to dynamic loading regardless of the experimental diet. The effects of voluntary wheel running on cortical bone are site-dependent along the femoral bone, with different measurement techniques showing conflicting results.
4. The effects of voluntary wheel running seem to be diet-dependent: voluntary wheel runnning was positively associated with cross sectional area in the metaphysis and cortical thickness in the femoral shaft under the high-fat diet, and negatively associated with these parameters under the control diet. Voluntary wheel running enlarged the marrow cavity under the control diet but contracted it under the high-fat diet.

YHTEENVETO (FINNISH SUMMARY)

Luun mukautuminen fyysiseen aktiivisuuteen ja ravinnon aikaansaamaan lihavuuteen

Selkärankaisten tukiranka muodostuu pääosin luukudoksesta, jota muokataan - vanhaa poistetaan ja uutta muodostetaan - koko elinkaaren ajan. Ihmisillä osteoporoosi (luukato) ja lihavuus ovat kaksi toisiinsa läheisesti liittyvää ruumiinrakenteen epätasapainotilaa, jotka lisääntyvät väestössä maailmanlaajuisesti. Useissa tutkimuksissa on osoitettu liikunnan suojaavan luustoa osteoporoosilta ja vähentävän lihavuuteen liittyviä terveysongelmia. Mekanismeja, jotka ovat liikunnan aikaansaamien suojavaikutusten taustalla, ei kuitenkaan vielä täysin tunneta. Tässä työssä näitä mekanismeja selvitettiin sekä kaksostutkimuksen että koeläintutkimuksen keinoin.

Kaksostutkimuksessa sääriluun rakenteellisia ominaisuuksia mitattiin kaksospareilta, joista toinen parikki oli harrastanut vapaa-ajan liikuntaa selvästi enemmän kuin toinen viimeksi kuluneen 30 vuoden aikana. Tutkimuksen tulokset osoittivat, että pitkään kestänyt liikunnallinen aktiivisuus oli yhteydessä paksumpaan kuoriluuhun, kuoriluun suurempaan poikkipinta-alaan ja hohkaluun suurempaan tiheyteen. Identtisten kaksosten tulokset vahvistivat sen, että vapaa-ajan liikuntaharrastus, perimästä riippumatta, vahvistaa luun rakennetta.

Eläinkokeissa tutkittiin rasvapitoisen ravinnon aikaansaaman lihavuuden ja vapaaehtoisen juoksupyörässä juoksun sekä niiden yhdistelmän vaikutuksia hiiren reisiluun ja selkänikamien rakenteeseen ja mekaaniseen lujuuteen. Tämän osatutkimuksen tulokset osoittivat sekä lihavuuden että vapaaehtoisen juoksukuormituksen vaikuttavan hiiren luun ominaisuuksiin. Lisääntyneellä ruumiin painolla oli kuitenkin selvästi suurempi vaikutus kuin juoksukuormituksella. Lihavien hiirten reisiluut olivat kooltaan suurempia ja niiden mineraalimassa oli suurempi kuin normaalia ravintoa syöneiden, kevyempien hiirten. Samoin eräät luun lujuutta kuvaavat suureet osoittivat lihavien hiirten luiden olevan vahvempia. Kun hiirten luun mikrorakennetta tutkittiin tarkemmin, havaittiin, että sekä reisiluussa että selkänikamissa lihavien hiirten hohkaluun tiheys oli suurempi kuin kontrollihiirillä. Tätä eroa ei havaittu kuoriluussa.

Vapaaehtoinen juoksukuormitus oli yhteydessä reisiluun vähäisempään tiheyteen ja lujuuteen erityisesti normaalia ravintoa syöneillä, kevyemmillä hiirillä. Lihavilla hiirillä vapaaehtoinen juoksukuormitus pienensi luuydinkanavaa, lisäsi hohkaluun tiheyttä ja aiheutti siirtymää sauvamaisesta rakenteesta lujemman, levymäisen rakenteen suuntaan.

Eläinkokeen tulokset osoittivat, että hiiren luu mukautuu sekä lisääntyneeseen ruumiin painoon että juoksukuormitukseen. Mukautumista tapahtuu paikallisesti sekä luun makro- että mikrorakenteissa pyrkimyksenä säilyttää luun lujuus kulloistenkin vaatimusten mukaisena.

REFERENCES

Adami, S., Gatti, D., Viapiana, O., Fiore, C. E., Nuti, R., Luisetto, G., Ponte, M., Rossini, M., and BONTURNO Study Group. 2008. Physical activity and bone turnover markers: a cross-sectional and a longitudinal study. Calcif.Tissue Int. 83:388-392.

Adams, J. E. 2009. Quantitative computed tomography. Eur.J.Radiol. 71:415-424.

Aguirre, J. I., Plotkin, L. I., Stewart, S. A., Weinstein, R. S., Parfitt, A. M., Manolagas, S. C., and Bellido, T. 2006. Osteocyte apoptosis is induced by weightlessness in mice and precedes osteoclast recruitment and bone loss. J.Bone Miner.Res. 21:605-615.

Ahlborg, H. G., Johnell, O., Turner, C. H., Rannevik, G., and Karlsson, M. K. 2003. Bone loss and bone size after menopause. N.Engl.J.Med. 349:327-334.

Ahola, R., Korpelainen, R., Vainionpää, A., Leppaluoto, J., and Jämsä, T. 2009. Time-course of exercise and its association with 12-month bone changes. BMC Musculoskelet.Disord. 10:e138.

Akhter, M. P., Lund, A. D., and Gairola, C. G. 2005. Bone biomechanical property deterioration due to tobacco smoke exposure. Calcif.Tissue Int. 77:319-326.

Albanese, C. V., Diessel, E., and Genant, H. K. 2003. Clinical applications of body composition measurements using DXA. J.Clin.Densitom. 6:75-85.

Alberich-Bayarri, A., Marti-Bonmati, L., Angeles Perez, M., Sanz-Requena, R., Lerma-Garrido, J. J., Garcia-Marti, G., and Moratal, D. 2010. Assessment of 2D and 3D fractal dimension measurements of trabecular bone from high-spatial resolution magnetic resonance images at 3 T. Med.Phys. 37:4930-4937.

Alexander, C. 1995. Diagnosis and treatment of osteoporosis. Curr.Opin.Rheumatol. 7:240-242.

Almstedt Shoepe, H., and Snow, C. M. 2005. Oral contraceptive use in young women is associated with lower bone mineral density than that of controls. Osteoporos.Int. 16:1538-1544.

Alwis, G., Linden, C., Ahlborg, H. G., Dencker, M., Gardsell, P., and Karlsson, M. K. 2008a. A 2-year school-based exercise programme in pre-pubertal boys induces skeletal benefits in lumbar spine. Acta Paediatr. 97:1564-1571.

Alwis, G., Linden, C., Stenevi-Lundgren, S., Ahlborg, H. G., Besjakov, J., Gardsell, P., and Karlsson, M. K. 2008b. A one-year exercise intervention program in pre-pubertal girls does not influence hip structure. BMC Musculoskelet.Disord. 9:e9.

Amar, S., Zhou, Q., Shaik-Dasthagirisaheb, Y., and Leeman, S. 2007. Diet-induced obesity in mice causes changes in immune responses and bone loss manifested by bacterial challenge. Proc.Natl.Acad.Sci.U.S.A. 104:20466-20471.

Ammann, P. 2003. Determining factors of bone mechanical resistance. Therapie. 58:403-407.

Ammann, P., and Rizzoli, R. 2003. Bone strength and its determinants. Osteoporos.Int. 14 Suppl 3:S13-18.

Andersen, T. L., Sondergaard, T. E., Skorzynska, K. E., Dagnaes-Hansen, F., Plesner, T. L., Hauge, E. M., Plesner, T., and Delaisse, J. M. 2009. A physical mechanism for coupling bone resorption and formation in adult human bone. Am.J.Pathol. 174:239-247.

Andreoli, A., Scalzo, G., Masala, S., Tarantino, U., and Guglielmi, G. 2009. Body composition assessment by dual-energy X-ray absorptiometry (DXA). Radiol.Med. 114:286-300.

Anumula, S., Wehrli, S. L., Magland, J., Wright, A. C., and Wehrli, F. W. 2010. Ultra-short echo-time MRI detects changes in bone mineralization and water content in OVX rat bone in response to alendronate treatment. Bone. 46:1391-1399.

Anumula, S., Magland, J., Wehrli, S. L., Zhang, H., Ong, H., Song, H. K., and Wehrli, F. W. 2006. Measurement of phosphorus content in normal and osteomalacic rabbit bone by solid-state 3D radial imaging. Magn.Reson.Med. 56:946-952.

Arden, N. K., Baker, J., Hogg, C., Baan, K., and Spector, T. D. 1996. The heritability of bone mineral density, ultrasound of the calcaneus and hip axis length: a study of postmenopausal twins. J.Bone Miner.Res. 11:530-534.

Arlot, M. E., Jiang, Y., Genant, H. K., Zhao, J., Burt-Pichat, B., Roux, J. P., Delmas, P. D., and Meunier, P. J. 2008. Histomorphometric and microCT analysis of bone biopsies from postmenopausal osteoporotic women treated with strontium ranelate. J.Bone Miner.Res. 23:215-222.

Arnett, T. R. 2010. Acidosis, hypoxia and bone. Arch.Biochem.Biophys. 503:103-109.

Arnett, T. R., Gibbons, D. C., Utting, J. C., Orriss, I. R., Hoebertz, A., Rosendaal, M., and Meghji, S. 2003. Hypoxia is a major stimulator of osteoclast formation and bone resorption. J.Cell.Physiol. 196:2-8.

Ashizawa, N., Nonaka, K., Michikami, S., Mizuki, T., Amagai, H., Tokuyama, K., and Suzuki, M. 1999. Tomographical description of tennis-loaded radius: reciprocal relation between bone size and volumetric BMD. J.Appl.Physiol. 86:1347-1351.

Astrup, A., Dyerberg, J., Selleck, M., and Stender, S. 2008. Nutrition transition and its relationship to the development of obesity and related chronic diseases. Obes.Rev. 9 Suppl 1:48-52.

Attie, K. M., Ramirez, N. R., Conte, F. A., Kaplan, S. L., and Grumbach, M. M. 1990. The pubertal growth spurt in eight patients with true precocious puberty and growth hormone deficiency: evidence for a direct role of sex steroids. J.Clin.Endocrinol.Metab. 71:975-983.

Aubertin-Leheudre, M., Lord, C., Labonte, M., Khalil, A., and Dionne, I. J. 2008. Relationship between sarcopenia and fracture risks in obese postmenopausal women. J.Women Aging. 20:297-308.

Bailey, C. A., Kukuljan, S., and Daly, R. M. 2010. Effects of lifetime loading history on cortical bone density and its distribution in middle-aged and older men. Bone. 47:673-680.

Bailey, C. A., and Brooke-Wavell, K. 2008. Exercise for optimising peak bone mass in women. Proc.Nutr.Soc. 67:9-18.

Bakker, I., Twisk, J. W., Van Mechelen, W., and Kemper, H. C. 2003. Fat-free body mass is the most important body composition determinant of 10-yr longitudinal development of lumbar bone in adult men and women. J.Clin.Endocrinol.Metab. 88:2607-2613.

Banu, J., Bhattacharya, A., Rahman, M., O'Shea, M., and Fernandes, G. 2006. Effects of conjugated linoleic acid and exercise on bone mass in young male Balb/C mice. Lipids Health.Dis. 23:5-7.

Banu, J., Orhii, P. B., Okafor, M. C., Wang, L., and Kalu, D. N. 2001. Analysis of the effects of growth hormone, exercise and food restriction on cancellous bone in different bone sites in middle-aged female rats. Mech.Ageing Dev. 122:849-864.

Banu, M. J., Orhii, P. B., Mejia, W., McCarter, R. J., Mosekilde, L., Thomsen, J. S., and Kalu, D. N. 1999. Analysis of the effects of growth hormone, voluntary exercise, and food restriction on diaphyseal bone in female F344 rats. Bone. 25:469-480.

Barou, O., Valentin, D., Vico, L., Tirode, C., Barbier, A., Alexandre, C., and Lafage-Proust, M. H. 2002. High-resolution three-dimensional micro-computed tomography detects bone loss and changes in trabecular architecture early: comparison with DEXA and bone histomorphometry in a rat model of disuse osteoporosis. Invest.Radiol. 37:40-46.

Basillais, A., Bensamoun, S., Chappard, C., Brunet-Imbault, B., Lemineur, G., Ilharreborde, B., Ho Ba Tho, M. C., and Benhamou, C. L. 2007. Three-dimensional characterization of cortical bone microstructure by microcomputed tomography: validation with ultrasonic and microscopic measurements. J.Orthop.Sci. 12:141-148.

Bass, S., Delmas, P. D., Pearce, G., Hendrich, E., Tabensky, A., and Seeman, E. 1999. The differing tempo of growth in bone size, mass, and density in girls is region-specific. J.Clin.Invest. 104:795-804.

Bass, S. L., Naughton, G., Saxon, L., Iuliano-Burns, S., Daly, R., Briganti, E. M., Hume, C., and Nowson, C. 2007. Exercise and calcium combined results in a greater osteogenic effect than either factor alone: a blinded randomized placebo-controlled trial in boys. J.Bone Miner.Res. 22:458-464.

Bass, S. L., Eser, P., and Daly, R. 2005. The effect of exercise and nutrition on the mechanostat. J.Musculoskelet.Neuronal Interact. 5:239-254.

Bass, S. L., Saxon, L., Daly, R. M., Turner, C. H., Robling, A. G., Seeman, E., and Stuckey, S. 2002. The effect of mechanical loading on the size and shape of bone in pre-, peri-, and postpubertal girls: a study in tennis players. J.Bone Miner.Res. 17:2274-2280.

Bauer, J. S., and Link, T. M. 2009. Advances in osteoporosis imaging. Eur.J.Radiol. 71:440-449.

Beaupied, H., Lespessailles, E., and Benhamou, C. L. 2007. Evaluation of macrostructural bone biomechanics. Joint Bone Spine. 74:233-239.

Beck, B. R. 2009a. Muscle forces or gravity--what predominates mechanical loading on bone? Introduction. Med.Sci.Sports Exerc. 41:2033-2036.

Beck, T. J. 2009b. Comparison of DXA hip structural analysis with volumetric QCT. J.Clin.Densitom. 12:260-261; author reply 262.

Beck, T. J. 2007. Extending DXA beyond bone mineral density: understanding hip structure analysis. Curr.Osteoporos.Rep. 5:49-55.

Begot, L., Collombet, J. M., Renault, S., Butigieg, X., Andre, C., Zerath, E., and Holy, X. 2010. Effects of High Phosphorus and/or Low Calcium Diets on Bone Tissue in Trained Male Rats. Med.Sci.Sports Exerc. 43:54-63.

Bell, K. L., Loveridge, N., Jordan, G. R., Power, J., Constant, C. R., and Reeve, J. 2000. A novel mechanism for induction of increased cortical porosity in cases of intracapsular hip fracture. Bone. 27:297-304.

Berard, A., Bravo, G., and Gauthier, P. 1997. Meta-analysis of the effectiveness of physical activity for the prevention of bone loss in postmenopausal women. Osteoporos.Int. 7:331-337.

Berecki-Gisolf, J., Hockey, R., and Dobson, A. 2008. Adherence to bisphosphonate treatment by elderly women. Menopause. 15:984-990.

Bergot, C., Wu, Y., Jolivet, E., Zhou, L. Q., Laredo, J. D., and Bousson, V. 2009. The degree and distribution of cortical bone mineralization in the human femoral shaft change with age and sex in a microradiographic study. Bone. 45:435-442.

Bergot, C., Laval-Jeante, A. M., Bouysse, S., and Laval-Jeantet, M. 1990. Changes in bone volume and mineral density during aging in humans. *In vitro* study on 80 subjects. Rev.Rhum.Mal.Osteoartic. 57:791-798.

Biewener, A. A. 1991. Musculoskeletal design in relation to body size. J.Biomech. 24 Suppl1:19-29.

Bikle, D. D., and Halloran, B. P. 1999. The response of bone to unloading. J.Bone Miner.Metab. 17:233-244.

Blake, G. M., and Fogelman, I. 2010. An update on dual-energy x-ray absorptiometry. Semin.Nucl.Med. 40:62-73.

Blake, G. M., Preston, N. G., Patel, R., Herd, R. J., and Fogelman, I. 1999. An unexpected change in DXA calibration not detected by routine quality control checks. Osteoporos.Int. 9:115-120.

Boel, L. W., Boldsen, J. L., and Melsen, F. 2007. Double lamellae in trabecular osteons: towards a new method for age estimation by bone microscopy. Homo. 58:269-277.

Bogl, L. H., Latvala, A., Kaprio, J., Sovijarvi, O., Rissanen, A., and Pietilainen, K. H. 2011. An investigation into the relationship between soft tissue body composition and bone mineral density in a young adult twin sample. J.Bone Miner.Res. 26:79-87.

Boivin, G., Farlay, D., Bala, Y., Doublier, A., Meunier, P. J., and Delmas, P. D. 2009. Influence of remodeling on the mineralization of bone tissue. Osteoporos.Int. 20:1023-1026.

Boivin, G., Bala, Y., Doublier, A., Farlay, D., Ste-Marie, L. G., Meunier, P. J., and Delmas, P. D. 2008. The role of mineralization and organic matrix in the microhardness of bone tissue from controls and osteoporotic patients. Bone. 43:532-538.

Boivin, G., and Meunier, P. J. 2003. The mineralization of bone tissue: a forgotten dimension in osteoporosis research. Osteoporos.Int. 14 Suppl 3:S19-24.

Boivin, G., and Meunier, P. J. 2002a. Changes in bone remodeling rate influence the degree of mineralization of bone. Connect.Tissue Res. 43:535-537.

Boivin, G., and Meunier, P. J. 2002b. The degree of mineralization of bone tissue measured by computerized quantitative contact microradiography. Calcif.Tissue Int. 70:503-511.

Bonewald, L. 2006. Osteocytes as multifunctional cells. J.Musculoskelet.Neuronal Interact. 6:331-333.

Bonewald, L. F. 2010. The Amazing Osteocyte. J.Bone Miner.Res. 26:229-238.

Bonewald, L. F. 2007. Osteocytes as dynamic multifunctional cells. Ann.N.Y.Acad.Sci. 1116:281-290.

Bonjour, J. P., Theintz, G., Buchs, B., Slosman, D., and Rizzoli, R. 1991. Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. J.Clin.Endocrinol.Metab. 73:555-563.

Bonnick, S. L. 2007a. Noninvasive assessments of bone strength. Curr.Opin.Endocrinol.Diabetes Obes. 14:451-457.

Bonnick, S. L. 2007b. HSA: beyond BMD with DXA. Bone. 41:S9-12.

Bonnick, S. L. 2002. Current controversies in bone densitometry. Curr.Opin.Rheumatol. 14:416-420.

Bonse, U., and Busch, F. 1996. X-ray computed microtomography (microCT) using synchrotron radiation (SR). Prog.Biophys.Mol.Biol. 65:133-169.

Boot, A. M., de Ridder, M. A., van der Sluis, I. M., van Slobbe, I., Krenning, E. P., and Keizer-Schrama, S. M. 2010. Peak bone mineral density, lean body mass and fractures. Bone. 46:336-341.

Borah, B., Dufresne, T., Nurre, J., Phipps, R., Chmielewski, P., Wagner, L., Lundy, M., Bouxsein, M., Zebaze, R., and Seeman, E. 2010. Risedronate reduces intracortical porosity in women with osteoporosis. J.Bone Miner.Res. 25:41-47.

Borah, B., Gross, G. J., Dufresne, T. E., Smith, T. S., Cockman, M. D., Chmielewski, P. A., Lundy, M. W., Hartke, J. R., and Sod, E. W. 2001. Three-dimensional microimaging (microMRI and microCT), finite element modeling, and rapid prototyping provide unique insights into bone architecture in osteoporosis. Anat.Rec. 265:101-110.

Borer, K. T., Fogleman, K., Gross, M., La New, J. M., and Dengel, D. 2007. Walking intensity for postmenopausal bone mineral preservation and accrual. Bone. 41:713-721.

Boskey, A. L., Spevak, L., and Weinstein, R. S. 2009. Spectroscopic markers of bone quality in alendronate-treated postmenopausal women. Osteoporos.Int. 20:793-800.

Boskey, A. L. 2006. Assessment of bone mineral and matrix using backscatter electron imaging and FTIR imaging. Curr.Osteoporos Rep. 4:71-75.

Boskey, A. L., DiCarlo, E., Paschalis, E., West, P., and Mendelsohn, R. 2005. Comparison of mineral quality and quantity in iliac crest biopsies from high- and low-turnover osteoporosis: an FT-IR microspectroscopic investigation. Osteoporos.Int. 16:2031-2038.

Bossy, E., Talmant, M., Peyrin, F., Akrout, L., Cloetens, P., and Laugier, P. 2004. An *in vitro* study of the ultrasonic axial transmission technique at the radius: 1-MHz velocity measurements are sensitive to both mineralization and intracortical porosity. J.Bone Miner.Res. 19:1548-1556.

Bourrin, S., Genty, C., Palle, S., Gharib, C., and Alexandre, C. 1994. Adverse effects of strenuous exercise: a densitometric and histomorphometric study in the rat. J.Appl.Physiol. 76:1999-2005.

Bousson, V., Peyrin, F., Bergot, C., Hausard, M., Sautet, A., and Laredo, J. D. 2004. Cortical bone in the human femoral neck: three-dimensional appearance and porosity using synchrotron radiation. J.Bone Miner.Res. 19:794-801.

Bousson, V., Meunier, A., Bergot, C., Vicaut, E., Rocha, M. A., Morais, M. H., Laval-Jeantet, A. M., and Laredo, J. D. 2001. Distribution of intracortical porosity in human midfemoral cortex by age and gender. J.Bone Miner.Res. 16:1308-1317.

Bousson, V., Bergot, C., Meunier, A., Barbot, F., Parlier-Cuau, C., Laval-Jeantet, A. M., and Laredo, J. D. 2000. CT of the middiaphyseal femur: cortical bone mineral density and relation to porosity. Radiology. 217:179-187.

Bouxsein, M. L., and Seeman, E. 2009. Quantifying the material and structural determinants of bone strength. Best Pract.Res.Clin.Rheumatol. 23:741-753.

Bouxsein, M. L., and Karasik, D. 2006. Bone geometry and skeletal fragility. Curr.Osteoporos Rep. 4:49-56.

Bower, A. L., Lang, D. H., Vogler, G. P., Vandenbergh, D. J., Blizard, D. A., Stout, J. T., McClearn, G. E., and Sharkey, N. A. 2006. QTL analysis of trabecular bone in BXD F2 and RI mice. J.Bone Miner.Res. 21:1267-1275.

Boyde, A., and Riggs, C. M. 1990. The quantitative study of the orientation of collagen in compact bone slices. Bone. 11:35-39.

Boyle, W. J., Simonet, W. S., and Lacey, D. L. 2003. Osteoclast differentiation and activation. Nature. 423:337-342.

Bozec, L., de Groot, J., Odlyha, M., Nicholls, B., and Horton, M. A. 2005a. Mineralised tissues as nanomaterials: analysis by atomic force microscopy. IEE Proc.Nanobiotechnol. 152:183-186.

Bozec, L., de Groot, J., Odlyha, M., Nicholls, B., Nesbitt, S., Flanagan, A., and Horton, M. 2005b. Atomic force microscopy of collagen structure in bone and dentine revealed by osteoclastic resorption. Ultramicroscopy. 105:79-89.

Brahmabhatt, V., Rho, J., Bernardis, L., Gillespie, R., and Ziv, I. 1998. The effects of dietary-induced obesity on the biomechanical properties of femora in male rats. Int.J.Obes.Relat.Metab.Disord. 22:813-818.

Braillon, P. M., and Serban, A. 2007. Bone mineral content and body composition in overweight children and adolescents. Pediatr.Res. 62:462-467.

Braillon, P. M. 2003. Annual changes in bone mineral content and body composition during growth. Horm.Res. 60:284-290.

Brandi, M. L. 2009. Microarchitecture, the key to bone quality. Rheumatology (Oxford). 48 Suppl 4:S3-8.

Breban, S., Chappard, C., Jaffre, C., Briot, K., and Benhamou, C. L. 2010. Anthropometry at birth as a strong determinant factor of young women bone status: Influence of high-level physical activity. Joint Bone Spine. 78:200-205.

Brennan, T. C., Rizzoli, R., and Ammann, P. 2009. Selective modification of bone quality by PTH, pamidronate, or raloxifene. J.Bone Miner.Res. 24:800-808.

Bromage, T. G., Goldman, H. M., McFarlin, S. C., Warshaw, J., Boyde, A., and Riggs, C. M. 2003. Circularly polarized light standards for investigations of collagen fiber orientation in bone. Anat.Rec.B.New Anat. 274:157-168.

Brown, L. B., Streeten, E. A., Shuldiner, A. R., Almasy, L. A., Peyser, P. A., and Mitchell, B. D. 2004. Assessment of sex-specific genetic and environmental effects on bone mineral density. Genet.Epidemiol. 27:153-161.

Budek, A. Z., Hoppe, C., Ingstrup, H., Michaelsen, K. F., Bugel, S., and Molgaard, C. 2007. Dietary protein intake and bone mineral content in adolescents-The Copenhagen Cohort Study. Osteoporos.Int. 18:1661-1667.

Buie, H. R., Campbell, G. M., Klinck, R. J., MacNeil, J. A., and Boyd, S. K. 2007. Automatic segmentation of cortical and trabecular compartments based on a dual threshold technique for *in vivo* micro-CT bone analysis. Bone. 41:505-515.

Burghardt, A. J., Kazakia, G. J., Sode, M., de Papp, A. E., Link, T. M., and Majumdar, S. 2010. A longitudinal HR-pQCT study of alendronate treatment in postmenopausal women with low bone density: Relations among density, cortical and trabecular microarchitecture, biomechanics, and bone turnover. J.Bone Miner.Res. 25:2282-2295.

Burghardt, A. J., Kazakia, G. J., Laib, A., and Majumdar, S. 2008. Quantitative assessment of bone tissue mineralization with polychromatic micro-computed tomography. Calcif.Tissue Int. 83:129-138.

Burr, D. 2003. Microdamage and bone strength. Osteoporos.Int. 14 Suppl 5:S67-72.

Burr, D. B., and Allen, M. R. 2008. Low bone turnover and microdamage? How and where to assess it? J.Bone Miner.Res. 23:1150-1151; author reply 1152-1153.

Burr, D. B. 2002. Targeted and nontargeted remodeling. Bone. 30:2-4.

Burr, D. B., Turner, C. H., Naick, P., Forwood, M. R., Ambrosius, W., Hasan, M. S., and Pidaparti, R. 1998. Does microdamage accumulation affect the mechanical properties of bone? J.Biomech. 31:337-345.

Burr, D. B., Forwood, M. R., Fyhrie, D. P., Martin, R. B., Schaffler, M. B., and Turner, C. H. 1997. Bone microdamage and skeletal fragility in osteoporotic and stress fractures. J.Bone Miner.Res. 12:6-15.

Burr, D. B. 1993. Remodeling and the repair of fatigue damage. Calcif.Tissue Int. 53 Suppl 1:S75-80; discussion S80-81.

Burr, D. B., Martin, R. B., Schaffler, M. B., and Radin, E. L. 1985. Bone remodeling in response to *in vivo* fatigue microdamage. J.Biomech. 18:189-200.

Burstein, A. H., Zika, J. M., Heiple, K. G., and Klein, L. 1975. Contribution of collagen and mineral to the elastic-plastic properties of bone. J.Bone Joint Surg.Am. 57:956-961.

Canalis, E., Giustina, A., and Bilezikian, J. P. 2007. Mechanisms of anabolic therapies for osteoporosis. N.Engl.J.Med. 357:905-916.

Cano, J., Campo, J., Vaquero, J. J., Martinez Gonzalez, J. M., and Bascones, A. 2008. High resolution image in bone biology II. Review of the literature. Med.Oral Patol.Oral Cir.Bucal. 13:e31-35.

Cano, J., Campo, J., Vaquero, J. J., Martinez, J. M., and Bascones, A. 2007. High resolution image in bone biology I. Review of the literature. Med.Oral Patol.Oral Cir.Bucal. 12:e454-458.

Cao, H., Nazarian, A., Ackerman, J. L., Snyder, B. D., Rosenberg, A. E., Nazarian, R. M., Hrovat, M. I., Dai, G., Mintzopoulos, D., and Wu, Y. 2010. Quantitative (31)P NMR spectroscopy and (1)H MRI measurements of bone mineral and matrix density differentiate metabolic bone diseases in rat models. Bone. 46:1582-1590.

Cao, J. J., Gregoire, B. R., and Gao, H. 2009. High-fat diet decreases cancellous bone mass but has no effect on cortical bone mass in the tibia in mice. Bone. 44: 1097-1104.

Cardoso, L., Herman, B. C., Verborgt, O., Laudier, D., Majeska, R. J., and Schaffler, M. B. 2009. Osteocyte apoptosis controls activation of intracortical resorption in response to bone fatigue. J.Bone Miner.Res. 24:597-605.

Castillo, A. B., Alam, I., Tanaka, S. M., Levenda, J., Li, J., Warden, S. J., and Turner, C. H. 2006. Low-amplitude, broad-frequency vibration effects on cortical bone formation in mice. Bone. 39:1087-1096.

Chae, H. J., Park, R. K., Chung, H. T., Kang, J. S., Kim, M. S., Choi, D. Y., Bang, B. G., and Kim, H. R. 1997. Nitric oxide is a regulator of bone remodelling. J.Pharm.Pharmacol. 49:897-902.

Chan, K., Qin, L., Lau, M., Woo, J., Au, S., Choy, W., Lee, K., and Lee, S. 2004. A randomized, prospective study of the effects of Tai Chi Chun exercise on bone mineral density in postmenopausal women. Arch.Phys.Med.Rehabil. 85:717-722.

Chang, G., Regatte, R. R., and Schweitzer, M. E. 2009. Olympic fencers: adaptations in cortical and trabecular bone determined by quantitative computed tomography. Osteoporos.Int. 20:779-785.

Chang, M. K., Raggatt, L. J., Alexander, K. A., Kuliwaba, J. S., Fazzalari, N. L., Schroder, K., Maylin, E. R., Ripoll, V. M., Hume, D. A., and Pettit, A. R. 2008. Osteal tissue macrophages are intercalated throughout human and mouse bone lining tissues and regulate osteoblast function *in vitro* and in vivo. J.Immunol. 181:1232-1244.

Chao, D., Espeland, M. A., Farmer, D., Register, T. C., Lenchik, L., Applegate, W. B., and Ettinger, WH. Jr. 2000. Effect of voluntary weight loss on bone mineral density in older overweight women. J.Am.Geriatr.Soc. 48:753-759.

Chappard, C., Bousson, V., Bergot, C., Mitton, D., Marchadier, A., Moser, T., Benhamou, C. L., and Laredo, J. D. 2010. Prediction of femoral fracture load: cross-sectional study of texture analysis and geometric measurements on plain radiographs versus bone mineral density. Radiology. 255:536-543.

Chappard, D., Basle, M. F., Legrand, E., and Audran, M. 2008. Trabecular bone microarchitecture: a review. Morphologie. 92:162-170.

Chapurlat, R. D. 2009. Bone microdamage. Osteoporos.Int. 20:1033-1035.

Chapurlat, R. D., and Delmas, P. D. 2009. Bone microdamage: a clinical perspective. Osteoporos.Int. 20:1299-1308.

Charras, G. T., and Horton, M. A. 2002a. Determination of cellular strains by combined atomic force microscopy and finite element modeling. Biophys.J. 83:858-879.

Charras, G. T., and Horton, M. A. 2002b. Single cell mechanotransduction and its modulation analyzed by atomic force microscope indentation. Biophys.J. 82:2970-2981.

Charras, G. T., Lehenkari, P. P., and Horton, M. A. 2001. Atomic force microscopy can be used to mechanically stimulate osteoblasts and evaluate cellular strain distributions. Ultramicroscopy. 86:85-95.

Chavassieux, P., Seeman, E., and Delmas, P. D. 2007. Insights into material and structural basis of bone fragility from diseases associated with fractures: how determinants of the biomechanical properties of bone are compromised by disease. Endocr.Rev. 28:151-164.

Chen, H., Zhou, X., Shoumura, S., Emura, S., and Bunai, Y. 2010. Age- and gender-dependent changes in three-dimensional microstructure of cortical and trabecular bone at the human femoral neck. Osteoporos.Int. 21:627-636.

Chen, Q., Kaji, H., Iu, M. F., Nomura, R., Sowa, H., Yamauchi, M., Tsukamoto, T., Sugimoto, T., and Chihara, K. 2003. Effects of an excess and a deficiency of endogenous parathyroid hormone on volumetric bone mineral density and bone geometry determined by peripheral quantitative computed tomography in female subjects. J.Clin.Endocrinol.Metab. 88:4655-4658.

Chen, S. C., Lai, C. H., Chan, W. P., Huang, M. H., Tsai, H. W., and Chen, J. J. 2005. Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. Disabil.Rehabil. 27:1337-1341.

Chevalley, T., Bonjour, J. P., Ferrari, S., and Rizzoli, R. 2008. High-protein intake enhances the positive impact of physical activity on BMC in prepubertal boys. J.Bone Miner.Res. 23:131-142.

Clark, E. M., and Tobias, J. H. 2011. Fat mass is a positive predictor of bone mass in adolescents. J.Bone Miner.Res. 25:1544-1554.

Clark, E. M., Ness, A. R., and Tobias, J. H. 2008. Vigorous physical activity increases fracture risk in children irrespective of bone mass: a prospective study of the independent risk factors for fractures in healthy children. J.Bone Miner.Res. 23:1012-1022.

Clark, E. M., Ness, A. R., and Tobias, J. H. 2006. Adipose tissue stimulates bone growth in prepubertal children. J.Clin.Endocrinol.Metab. 91:2534-2541.

Clarke, B. 2008. Normal bone anatomy and physiology. Clin.J.Am.Soc.Nephrol. 3 Suppl 3:S131-139.

Cobayashi, F., Lopes, L. A., and Taddei, J. A. 2005. Bone mineral density in overweight and obese adolescents. J.Pediatr.(Rio J). 81:337-342.

Cock, T. A., and Auwerx, J. 2003. Leptin: cutting the fat off the bone. Lancet. 362:1572-1574.

Confavreux, C. B. 2011. Bone: from a reservoir of minerals to a regulator of energy metabolism. Kidney Int. 121: S14-9.

Confavreux, C. B., Levine, R. L., and Karsenty, G. 2009. A paradigm of integrative physiology, the crosstalk between bone and energy metabolisms. Mol.Cell.Endocrinol. 310:21-29.

Congiu, T., and Pazzaglia, U. E. 2011. The sealed osteons of cortical diaphyseal bone. early observations revisited with scanning electron microscopy. Anat.Rec.(Hoboken). 294:193-198 .

Constantini, N. W., Dubnov-Raz, G., Chodik, G., Rozen, G. S., Giladi, A., and Ish-Shalom, S. 2009. Physical activity and bone mineral density in adolescents with vitamin D deficiency. Med.Sci.Sports Exerc. 42: 646-650.

Cooper, C., Harvey, N., Javaid, K., Hanson, M., and Dennison, E. 2008. Growth and bone development. Nestle Nutr.Workshop Ser.Pediatr.Program. 61:53-68.

Cooper, C., Westlake, S., Harvey, N., Javaid, K., Dennison, E., and Hanson, M. 2006. Review: developmental origins of osteoporotic fracture. Osteoporos.Int. 17:337-347.

Cooper, D., Turinsky, A., Sensen, C., and Hallgrimsson, B. 2007. Effect of voxel size on 3D micro-CT analysis of cortical bone porosity. Calcif.Tissue Int. 80:211-219.

Cooper, D. M., Matyas, J. R., Katzenberg, M. A., and Hallgrimsson, B. 2004. Comparison of microcomputed tomographic and microradiographic measurements of cortical bone porosity. Calcif.Tissue Int. 74:437-447.

Cooper, D. M., Turinsky, A. L., Sensen, C. W., and Hallgrimsson, B. 2003. Quantitative 3D analysis of the canal network in cortical bone by micro-computed tomography. Anat.Rec.B.New Anat. 274:169-179.

Corwin, R. L., Hartman, T. J., Maczuga, S. A., and Graubard, B. I. 2006. Dietary saturated fat intake is inversely associated with bone density in humans: analysis of NHANES III. J.Nutr. 136:159-165.

Courteix, D., Rieth, N., Thomas, T., Van Praagh, E., Benhamou, C. L., Collomp, K., Lespessailles, E., and Jaffre, C. 2007. Preserved bone health in adolescent elite rhythmic gymnasts despite hypoleptinemia. Horm.Res. 68:20-27.

Courtland, H. W., Nasser, P., Goldstone, A. B., Spevak, L., Boskey, A. L., and Jepsen, K. J. 2008. Fourier transform infrared imaging microspectroscopy and tissue-level mechanical testing reveal intraspecies variation in mouse bone mineral and matrix composition. Calcif.Tissue Int. 83:342-353.

Cousins, J. M., Petit, M. A., Paudel, M. L., Taylor, B. C., Hughes, J. M., Cauley, J. A., Zmuda, J. M., Cawthon, P. M., Ensrud, K. E., and Osteoporotic Fractures in Men (MrOS) Study Group. 2010. Muscle power and physical activity are associated with bone strength in older men: The osteoporotic fractures in men study. Bone. 47:205-211.

Currey, J. D. 2005. Bone architecture and fracture. Curr.Osteoporos Rep. 3:52-56.

Currey, J. D. 2003. How well are bones designed to resist fracture? J.Bone Miner.Res. 18:591-598.

Cvijetic, S., Colic Baric, I., and Satalic, Z. 2010. Influence of heredity and environment on peak bone density: a parent-offspring study. J.Clin.Densitom. 13:301-306.

Dalen, N., Laftman, P., Ohlsen, H., and Stromberg, L. 1985. The effect of athletic activity on the bone mass in human diaphyseal bone. Orthopedics. 8:1139-1141.

Dallas, S. L., and Bonewald, L. F. 2010. Dynamics of the transition from osteoblast to osteocyte. Ann.N.Y.Acad.Sci. 1192:437-443.

Dalle Carbonare, L., and Giannini, S. 2004. Bone microarchitecture as an important determinant of bone strength. J.Endocrinol.Invest. 27:99-105.

Daly, R. M., Ahlborg, H. G., Ringsberg, K., Gardsell, P., Sernbo, I., and Karlsson, M. K. 2008a. Association between changes in habitual physical activity and changes in bone density, muscle strength, and functional performance in elderly men and women. J.Am.Geriatr.Soc. 56:2252-2260.

Daly, R. M., Petrass, N., Bass, S., and Nowson, C. A. 2008b. The skeletal benefits of calcium- and vitamin D3-fortified milk are sustained in older men after withdrawal of supplementation: an 18-mo follow-up study. Am.J.Clin.Nutr. 87:771-777.

Daly, R. M. 2007. The effect of exercise on bone mass and structural geometry during growth. Med.Sport.Sci. 51:33-49.

Daly, R. M., Bass, S., and Nowson, C. 2006. Long-term effects of calcium-vitamin-D3-fortified milk on bone geometry and strength in older men. Bone. 39:946-953.

Daly, R. M., and Bass, S. L. 2006. Lifetime sport and leisure activity participation is associated with greater bone size, quality and strength in older men. Osteoporos.Int. 17:1258-1267.

Damilakis, J., Adams, J. E., Guglielmi, G., and Link, T. M. 2010. Radiation exposure in X-ray-based imaging techniques used in osteoporosis. Eur.Radiol. 20:2707-2714.

Danielson, M. E., Cauley, J. A., Baker, C. E., Newman, A. B., Dorman, J. S., Towers, J. D., and Kuller, L. H. 1999. Familial resemblance of bone mineral density (BMD) and calcaneal ultrasound attenuation: the BMD in mothers and daughters study. J.Bone Miner.Res. 14:102-110.

Davison, K. S., Siminoski, K., Adachi, J. D., Hanley, D. A., Goltzman, D., Hodsman, A. B., Josse, R., Kaiser, S., Olszynski, W. P., Papaioannou, A., Ste-Marie, L. G., Kendler, D. L., Tenenhouse, A., and Brown, J. P. 2006. Bone strength: the whole is greater than the sum of its parts. Semin.Arthritis Rheum. 36:22-31.

De Bono, S., Schoenmakers, I., Ceesay, M., Mendy, M., Laskey, M. A., Cole, T. J., and Prentice, A. 2010. Birth weight predicts bone size in young adulthood at cortical sites in men and trabecular sites in women from The Gambia. Bone. 46:1316-1321.

Delany, A. M., Kalajzic, I., Bradshaw, A. D., Sage, E. H., and Canalis, E. 2003. Osteonectin-null mutation compromises osteoblast formation, maturation, and survival. Endocrinology. 144:2588-2596.

Delmas, P. D. 2000. Do we need to change the WHO definition of osteoporosis? 11:189-191.

Dempster, D. W., Ferguson-Pell, M. W., Mellish, R. W., Cochran, G. V., Xie, F., Fey, C., Horbert, W., Parisien, M., and Lindsay, R. 1993. Relationships between bone structure in the iliac crest and bone structure and strength in the lumbar spine. Osteoporos.Int. 3:90-96.

Dequeker, J., Nijs, J., Verstraeten, A., Geusens, P., and Gevers, G. 1987. Genetic determinants of bone mineral content at the spine and radius: a twin study. Bone. 8:207-209.

Deriaz, O., Najafi, B., Ballabeni, P., Crettenand, A., Gobelet, C., Aminian, K., Rizzoli, R., and Gremion, G. 2010. Proximal tibia volumetric bone mineral density is correlated to the magnitude of local acceleration in male long-distance runners. J.Appl.Physiol. 108:852-857.

Derman, O., Cinemre, A., Kanbur, N., Dogan, M., Kilic, M., and Karaduman, E. 2008. Effect of swimming on bone metabolism in adolescents. Turk.J.Pediatr. 50:149-154.

Devlin, M. J., Stetter, C. M., Lin, H. M., Beck, T. J., Legro, R. S., Petit, M. A., Lieberman, D. E., and Lloyd, T. 2010. Peripubertal estrogen levels and physical activity affect femur geometry in young adult women. Osteoporos.Int. 21:609-617.

Diab, T., Condon, K. W., Burr, D. B., and Vashishth, D. 2006. Age-related change in the damage morphology of human cortical bone and its role in bone fragility. Bone. 38:427-431.

Dimarco, N. M., Dart, L., and Sanborn, C. B. 2007. Modified activity-stress paradigm in an animal model of the female athlete triad. J.Appl.Physiol. 103:1469-1478.

Ding, M., Odgaard, A., Linde, F., and Hvid, I. 2002. Age-related variations in the microstructure of human tibial cancellous bone. J.Orthop.Res. 20:615-621.

DiVasta, A. D., Feldman, H. A., Quach, A. E., Balestrino, M., and Gordon, C. M. 2009. The effect of bed rest on bone turnover in young women hospitalized for anorexia nervosa: a pilot study. J.Clin.Endocrinol.Metab. 94:1650-1655.

Docheva, D., Padula, D., Popov, C., Mutschler, W., Clausen-Schaumann, H., and Schieker, M. 2008. Researching into the cellular shape, volume and elasticity of mesenchymal stem cells, osteoblasts and osteosarcoma cells by atomic force microscopy. J.Cell.Mol.Med. 12:537-552.

Dogan, M., Derman, O., Oksuz-Kanbur, N., Akgul, S., and Kutluk, T. 2009. The effects of nutrition and physical activity on bone development in male adolescents. Turk.J.Pediatr. 51:545-550.

Domon, T., Suzuki, R., Takata, K., Yamazaki, Y., Takahashi, S., Yamamoto, T., and Wakita, M. 2001. The nature and function of mononuclear cells on the resorbed surfaces of bone in the reversal phase during remodeling. Ann.Anat. 183:103-110.

Donnelly, E. 2010. Methods for Assessing Bone Quality: A Review. Clin.Orthop.Relat.Res. 469:2128-2138.

Donnelly, E., Baker, S. P., Boskey, A. L., and van der Meulen, M. C. 2006. Effects of surface roughness and maximum load on the mechanical properties of cancellous bone measured by nanoindentation. J.Biomed.Mater.Res.A. 77:426-435.

Dourmashkin, J. T., Chang, G. Q., Gayles, E. C., Hill, J. O., Fried, S. K., Julien, C., and Leibowitz, S. F. 2005. Different forms of obesity as a function of diet composition. Int.J.Obes.(Lond). 29:1368-1378.

Downey, P. A., and Siegel, M. I. 2006. Bone biology and the clinical implications for osteoporosis. Phys.Ther. 86:77-91.

Ducher, G., Bass, S. L., Saxon, L., and Daly, R. M. 2010. Effects of repetitive loading on the growth-induced changes in bone mass and cortical bone geometry: a 12-month study in pre/peri- and post-menarcheal tennis players. J.Bone Miner.Res. (Epub ahead of print).

Ducher, G., Bass, S. L., Naughton, G. A., Eser, P., Telford, R. D., and Daly, R. M. 2009a. Overweight children have a greater proportion of fat mass relative to muscle mass in the upper limbs than in the lower limbs: implications for bone strength at the distal forearm. Am.J.Clin.Nutr. 90:1104-1111.

Ducher, G., Daly, R. M., and Bass, S. L. 2009b. Effects of repetitive loading on bone mass and geometry in young male tennis players: a quantitative study using MRI. J.Bone Miner.Res. 24:1686-1692.

Ducher, G., Tournaire, N., Meddahi-Pelle, A., Benhamou, C. L., and Courteix, D. 2006. Short-term and long-term site-specific effects of tennis playing on trabecular and cortical bone at the distal radius. J.Bone Miner.Metab. 24:484-490.

Ducher, G., Courteix, D., Meme, S., Magni, C., Viala, J. F., and Benhamou, C. L. 2005. Bone geometry in response to long-term tennis playing and its relationship with muscle volume: a quantitative magnetic resonance imaging study in tennis players. Bone. 37:457-466.

Ducher, G., Prouteau, S., Courteix, D., and Benhamou, C. L. 2004. Cortical and trabecular bone at the forearm show different adaptation patterns in response to tennis playing. J.Clin.Densitom. 7:399-405.

Ducy, P., Amling, M., Takeda, S., Priemel, M., Schilling, A. F., Beil, F. T., Shen, J., Vinson, C., Rueger, J. M., and Karsenty, G. 2000. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. Cell. 100:197-207.

Dudley-Javoroski, S., and Shields, R. K. 2008a. Dose estimation and surveillance of mechanical loading interventions for bone loss after spinal cord injury. Phys.Ther. 88:387-396.

Dudley-Javoroski, S., and Shields, R. K. 2008b. Asymmetric bone adaptations to soleus mechanical loading after spinal cord injury. J.Musculoskelet.Neuronal Interact. 8:227-238.

Dufresne, T. 1998. Segmentation techniques for analysis of bone by three-dimensional computed tomographic imaging. Technol.Health Care. 6:351-359.

Dunlop, J. W., Hartmann, M. A., Brechet, Y. J., Fratzl, P., and Weinkamer, R. 2009. New suggestions for the mechanical control of bone remodeling. Calcif.Tissue Int. 85:45-54.

Duren, D. L., Sherwood, R. J., Choh, A. C., Czerwinski, S. A., Chumlea, W. C., Lee, M., Sun, S. S., Demerath, E. W., Siervogel, R. M., and Towne, B. 2007. Quantitative genetics of cortical bone mass in healthy 10-year-old children from the Fels Longitudinal Study. Bone. 40:464-470.

Eastell, R., Black, D. M., Boonen, S., Adami, S., Felsenberg, D., Lippuner, K., Cummings, S. R., Delmas, P. D., Palermo, L., Mesenbrink, P., Cauley, J. A., and HORIZON Pivotal Fracture Trial. 2009. Effect of once-yearly zoledronic acid five milligrams on fracture risk and change in femoral neck bone mineral density. J.Clin.Endocrinol.Metab. 94:3215-3225.

El Hage, R., Moussa, E., and Jacob, C. 2010. Femoral neck geometry in overweight and normal weight adolescent girls. J.Bone Miner.Metab. 28:595-600.

El Hage, R., Jacob, C., Moussa, E., Benhamou, C. L., and Jaffre, C. 2009a. Total body, lumbar spine and hip bone mineral density in overweight adolescent girls: decreased or increased? J.Bone Miner.Metab. 27:629-633.

El Hage, R., Jacob, C., Moussa, E., Groussard, C., Pineau, J. C., Benhamou, C. L., and Jaffre, C. 2009b. Influence of the weight status on bone mineral content and bone mineral density in a group of Lebanese adolescent girls. Joint Bone Spine. 76:680-684.

El Hage, R. P., Courteix, D., Benhamou, C. L., Jacob, C., and Jaffre, C. 2009c. Relative importance of lean and fat mass on bone mineral density in a group of adolescent girls and boys. Eur.J.Appl.Physiol. 105:759-764.

Engelke, K., Adams, J. E., Armbrecht, G., Augat, P., Bogado, C. E., Bouxsein, M. L., Felsenberg, D., Ito, M., Prevrhal, S., Hans, D. B., and Lewiecki, E. M. 2008. Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2007 ISCD Official Positions. J.Clin.Densitom. 11:123-162.

Engelke, K., Karolczak, M., Lutz, A., Seibert, U., Schaller, S., and Kalender, W. 1999. Micro-CT. Technology and application for assessing bone structure. Radiologe. 39:203-212.

Englund, U., Nordstrom, P., Nilsson, J., Bucht, G., Bjornstig, U., Hallmans, G., Svensson, O., and Pettersson, U. 2010. Physical activity in middle-aged women and hip fracture risk: the UFO study. Osteoporos.Int. 22:499-505.

Englund, U., Littbrand, H., Sondell, A., Bucht, G., and Pettersson, U. 2009. The beneficial effects of exercise on BMD are lost after cessation: a 5-year follow-up in older post-menopausal women. Scand.J.Med.Sci.Sports. 19:381-388.

Eppell, S. J., Tong, W., Katz, J. L., Kuhn, L., and Glimcher, M. J. 2001. Shape and size of isolated bone mineralites measured using atomic force microscopy. J.Orthop.Res. 19:1027-1034.

Eriksen, E. F. 2010. Cellular mechanisms of bone remodeling. Rev.Endocr Metab.Disord. 11:219-227.

Eser, P., Hill, B., Ducher, G., and Bass, S. 2009. Skeletal benefits after long-term retirement in former elite female gymnasts. J.Bone Miner.Res. 24:1981-1988.

Everts, V., de Vries, T. J., and Helfrich, M. H. 2009. Osteoclast heterogeneity: lessons from osteopetrosis and inflammatory conditions. Biochim.Biophys.Acta. 1792:757-765.

Fantner, G. E., Birkedal, H., Kindt, J. H., Hassenkam, T., Weaver, J. C., Cutroni, J. A., Bosma, B. L., Bawazer, L., Finch, M. M., Cidade, G. A., Morse, D. E., Stucky, G. D., and Hansma, P. K. 2004. Influence of the degradation of the organic matrix on the microscopic fracture behavior of trabecular bone. Bone. 35:1013-1022.

Farr, J. N., Lee, V. R., Blew, R. M., Lohman, T. G., and Going, S. B. 2011a. Quantifying bone-relevant activity and its relation to bone strength in girls. Med.Sci.Sports Exerc. 43: 476-483.

Farr, J. N., Tomas, R., Chen, Z., Lisse, J. R., Lohman, T. G., and Going, S. B. 2011b. Lower trabecular volumetric BMD at metaphyseal regions of weight-bearing bones is associated with prior fracture in young girls. J.Bone Miner.Res. 26:380-387.

Federman, D. D. 2006. The biology of human sex differences. N.Engl.J.Med. 354:1507-1514.

Feik, S. A., Thomas, C. D., and Clement, J. G. 1997. Age-related changes in cortical porosity of the midshaft of the human femur. J.Anat. 191:407-416.

Felson, D. T., Zhang, Y., Hannan, M. T., and Anderson, J. J. 1993. Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. J.Bone Miner.Res. 8:567-573.

Ferretti, J. L., Cointry, G. R., Capozza, R. F., and Frost, H. M. 2003. Bone mass, bone strength, muscle-bone interactions, osteopenias and osteoporoses. Mech.Ageing Dev. 124:269-279.

Ferretti, J. L., Cointry, G. R., Capozza, R. F., Capiglioni, R., and Chiappe, M. A. 2001. Analysis of biomechanical effects on bone and on the muscle-bone interactions in small animal models. J.Musculoskelet.Neuronal Interact. 1:263-274.

Feskanich, D., Willett, W., and Colditz, G. 2002. Walking and leisure-time activity and risk of hip fracture in postmenopausal women. JAMA. 288:2300-2306.

Fischer-Cripps, A. C. 2002. Nano-indentation. Springer; 1 edition.

Folkesson, J., Goldenstein, J., Carballido-Gamio, J., Kazakia, G., Burghardt, A. J., Rodriguez, A., Krug, R., de Papp, A. E., Link, T. M., and Majumdar, S. 2011. Longitudinal evaluation of the effects of alendronate on MRI bone microarchitecture in postmenopausal osteopenic women. Bone. 48:611-621.

Follet, H., Boivin, G., Rumelhart, C., and Meunier, P. J. 2004. The degree of mineralization is a determinant of bone strength: a study on human calcanei. Bone. 34:783-789.

Foo, L. H., Zhang, Q., Zhu, K., Ma, G., Hu, X., Greenfield, H., and Fraser, D. R. 2009. Low vitamin D status has an adverse influence on bone mass, bone turnover, and muscle strength in Chinese adolescent girls. J.Nutr. 139:1002-1007.

Forwood, M. R., Baxter-Jones, A. D., Beck, T. J., Mirwald, R. L., Howard, A., and Bailey, D. A. 2006. Physical activity and strength of the femoral neck during the adolescent growth spurt: a longitudinal analysis. Bone. 38:576-583.

Franz-Odendaal, T. A., Hall, B. K., and Witten, P. E. 2006. Buried alive: how osteoblasts become osteocytes. Dev.Dyn. 235:176-190.

Frost, H. M., Ferretti, J. L., and Jee, W. S. 1998. Perspectives: some roles of mechanical usage, muscle strength, and the mechanostat in skeletal physiology, disease, and research. Calcif.Tissue Int. 62:1-7.

Frost, H. M. 1996. Perspectives: a proposed general model of the "mechanostat" (suggestions from a new skeletal-biologic paradigm). Anat.Rec. 244:139-147.

Frost, H. M. 1964. Dynamics of bone remodeling in H.M. Frost (ed.): Bone Biodynamics. Little, Brown and Co., Boston.

Fujii, H., Noda, T., Sairenchi, T., and Muto, T. 2009. Daily intake of green and yellow vegetables is effective for maintaining bone mass in young women. Tohoku J.Exp.Med. 218:149-154.

Fuchs, R. K., and Snow, C. M. 2002. Gains in hip bone mass from high-impact training are maintained: a randomized controlled trial in children. J.Pediatr. 141:357-362.

Fukumoto, S., and Martin, T. J. 2009. Bone as an endocrine organ. Trends Endocrinol.Metab. 20:230-236.

Gallou-Kabani, C., Vige, A., Gross, M. S., Rabes, J. P., Boileau, C., Larue-Achagiotis, C., Tome, D., Jais, J. P., and Junien, C. 2007. C57BL/6J and A/J mice fed a high-fat diet delineate components of metabolic syndrome. Obesity (Silver Spring). 15:1996-2005.

Galusca, B., Zouch, M., Germain, N., Bossu, C., Frere, D., Lang, F., Lafage-Proust, M. H., Thomas, T., Vico, L., and Estour, B. 2008. Constitutional thinness: unusual human phenotype of low bone quality. J.Clin.Endocrinol.Metab. 93:110-117.

Ganss, B., Kim, R. H., and Sodek, J. 1999. Bone sialoprotein. Crit.Rev.Oral Biol.Med. 10:79-98.

Garland, T.,Jr, and Freeman, P. W. 2005. Selective breeding for high endurance running increases hindlimb symmetry. Evolution. 59:1851-1854.

Garnero, P., Borel, O., Gineyts, E., Duboeuf, F., Solberg, H., Bouxsein, M. L., Christiansen, C., and Delmas, P. D. 2006. Extracellular post-translational modifications of collagen are major determinants of biomechanical properties of fetal bovine cortical bone. Bone. 38:300-309.

Gasser, J. A. 1995. Assessing bone quantity by pQCT. Bone. 17:145S-154S.

Genant, H. K., and Jiang, Y. 2006. Advanced imaging assessment of bone quality. Ann.N.Y.Acad.Sci. 1068:410-428.

Genant, H. K., Engelke, K., Fuerst, T., Gluer, C. C., Grampp, S., Harris, S. T., Jergas, M., Lang, T., Lu, Y., Majumdar, S., Mathur, A., and Takada, M. 1996. Noninvasive assessment of bone mineral and structure: state of the art. J.Bone Miner.Res. 11:707-730.

Gentil, P., de Lima Lins, T. C., Lima, R. M., de Abreu, B. S., Grattapaglia, D., Bottaro, M., de Oliveira, R. J., and Pereira, R. W. 2009. Vitamin-d-receptor genotypes and bone-mineral density in postmenopausal women: interaction with physical activity. J.Aging Phys.Act. 17:31-45.

Geusens, P., Cantatore, F., Nijs, J., Proesmans, W., Emma, F., and Dequeker, J. 1991. Heterogeneity of growth of bone in children at the spine, radius and total skeleton. Growth Dev.Aging. 55:249-256.

Giangregorio, L., and Blimkie, C. J. 2002. Skeletal adaptations to alterations in weight-bearing activity: a comparison of models of disuse osteoporosis. Sports Med. 32:459-476.

Gielkens, P. F., Schortinghuis, J., de Jong, J. R., Huysmans, M. C., Leeuwen, M. B., Raghoebar, G. M., Bos, R. R., and Stegenga, B. 2008. A comparison of micro-CT, microradiography and histomorphometry in bone research. Arch.Oral Biol. 53:558-566.

Gilsanz, V. 1998. Bone density in children: a review of the available techniques and indications. Eur.J.Radiol. 26:177-182.

Gimble, J. M., Zvonic, S., Floyd, Z. E., Kassem, M., and Nuttall, M. E. 2006. Playing with bone and fat. J.Cell.Biochem. 98:251-266.

Giroux, S., Elfassihi, L., Clement, V., Bussieres, J., Bureau, A., Cole, D. E., and Rousseau, F. 2010. High-density polymorphisms analysis of 23 candidate genes for association with bone mineral density. Bone. 47:975-981.

Goldenstein, J., Kazakia, G., and Majumdar, S. 2010. *In vivo* evaluation of the presence of bone marrow in cortical porosity in postmenopausal osteopenic women. Ann.Biomed.Eng. 38:235-246.

Gomez-Ambrosi, J., Rodriguez, A., Catalan, V., and Fruhbeck, G. 2008. The bone-adipose axis in obesity and weight loss. Obes.Surg. 18:1134-1143.

Goodship, A. E., Cunningham, J. L., Oganov, V., Darling, J., Miles, A. W., and Owen, G. W. 1998. Bone loss during long term space flight is prevented by the application of a short term impulsive mechanical stimulus. Acta Astronaut. 43:65-75.

Gordon, J. A., Tye, C. E., Sampaio, A. V., Underhill, T. M., Hunter, G. K., and Goldberg, H. A. 2007. Bone sialoprotein expression enhances osteoblast differentiation and matrix mineralization *in vitro*. Bone. 41:462-473.

Goseki-Sone, M., Maruyama, R., Sogabe, N., and Hosoi, T. 2007. Effects of dietary lactose on long-term high-fat-diet-induced obesity in rats. Obesity (Silver Spring). 15:2605-2613.

Goulding, A., Taylor, R. W., Jones, I. E., Manning, P. J., and Williams, S. M. 2002. Spinal overload: a concern for obese children and adolescents? Osteoporos.Int. 13:835-840.

Goulding, A., Taylor, R. W., Jones, I. E., McAuley, K. A., Manning, P. J., and Williams, S. M. 2000. Overweight and obese children have low bone mass and area for their weight. Int.J.Obes.Relat.Metab.Disord. 24:627-632.

Goulding, A. 2007. Risk factors for fractures in normally active children and adolescents. Med.Sport.Sci. 51:102-120.

Gourion-Arsiquaud, S., Faibish, D., Myers, E., Spevak, L., Compston, J., Hodsman, A., Shane, E., Recker, R. R., Boskey, E. R., and Boskey, A. L. 2009. Use of FTIR spectroscopic imaging to identify parameters associated with fragility fracture. J.Bone Miner.Res. 24:1565-1571.

Gozansky, W. S., Van, P. RE., Jankowski, C. M., Schwartz, R. S., and Kohrt, W. M. 2005. Protection of bone mass by estrogens and raloxifene during exercise-induced weight loss. J.Clin.Endocrinol.Metab. 90:52-59.

Graham, J. S., Vomund, A. N., Phillips, C. L., and Grandbois, M. 2004. Structural changes in human type I collagen fibrils investigated by force spectroscopy. Exp.Cell Res. 299:335-342.

Greene, D. A., Wiebe, P. N., and Naughton, G. A. 2009. Influence of drop-landing exercises on bone geometry and biomechanical properties in prepubertal girls: a randomized controlled study. Calcif.Tissue Int. 85:94-103.

Greene, D. A., Naughton, G. A., Briody, J. N., Kemp, A., and Woodhead, H. 2006. Assessment of bone strength at differentially-loaded skeletal regions in adolescent middle-distance runners. J.Sci.Med.Sport. 9:221-230.

Greene, D. A., Naughton, G. A., Briody, J. N., Kemp, A., Woodhead, H., and Corrigan, L. 2005. Bone strength index in adolescent girls: does physical activity make a difference? Br.J.Sports Med. 39:622-627.

Griffith, J. F., Engelke, K., and Genant, H. K. 2010. Looking beyond bone mineral density : Imaging assessment of bone quality. Ann.N.Y.Acad.Sci. 1192:45-56.

Griffith, J. F., and Genant, H. K. 2008. Bone mass and architecture determination: state of the art. Best Pract.Res.Clin.Endocrinol.Metab. 22:737-764.

Gunter, K., Baxter-Jones, A. D., Mirwald, R. L., Almstedt, H., Fuchs, R. K., Durski, S., and Snow, C. 2008. Impact exercise increases BMC during growth: an 8-year longitudinal study. J.Bone Miner.Res. 23:986-993.

Haapasalo, H., Kontulainen, S., Sievänen, H., Kannus, P., Järvinen, M., and Vuori, I. 2000. Exercise-induced bone gain is due to enlargement in bone size without a change in volumetric bone density: a peripheral quantitative computed tomography study of the upper arms of male tennis players. Bone. 27:351-357.

Haapasalo, H., Kannus, P., Sievänen, H., Pasanen, M., Uusi-Rasi, K., Heinonen, A., Oja, P., and Vuori, I. 1998. Effect of long-term unilateral activity on bone mineral density of female junior tennis players. J.Bone Miner.Res. 13:310-319.

Haapasalo, H., Sievänen, H., Kannus, P., Heinonen, A., Oja, P., and Vuori, I. 1996a. Dimensions and estimated mechanical characteristics of the humerus after long-term tennis loading. J.Bone Miner.Res. 11:864-872.

Haapasalo, H., Kannus, P., Sievänen, H., Pasanen, M., Ussi-Rasi, K., Heinonen, A., Oja, P., and Vuori, I. 1996b. Development of mass, density, and estimated mechanical characteristics of bones in Caucasian females. J.Bone Miner.Res. 11:1151-1160.

Haiat, G., Naili, S., Grimal, Q., Talmant, M., Desceliers, C., and Soize, C. 2009. Influence of a gradient of material properties on ultrasonic wave propagation in cortical bone: application to axial transmission. J.Acoust.Soc.Am. 125:4043-4052.

Halade, G. V., Rahman, M. M., Williams, P. J., and Fernandes, G. 2010. High fat diet-induced animal model of age-associated obesity and osteoporosis. J.Nutr.Biochem. 21:1162-1169.

Halloran, B. P., Ferguson, V. L., Simske, S. J., Burghardt, A., Venton, L. L., and Majumdar, S. 2002. Changes in bone structure and mass with advancing age in the male C57BL/6J mouse. J.Bone Miner.Res. 17:1044-1050.

Hamilton, C. J., Thomas, S. G., and Jamal, S. A. 2010. Associations between leisure physical activity participation and cortical bone mass and geometry at the radius and tibia in a Canadian cohort of postmenopausal women. Bone. 46:774-779.

Hamrick, M. W., and Ferrari, S. L. 2008. Leptin and the sympathetic connection of fat to bone. Osteoporos.Int. 19:905-912.

Hamrick, M. W., Skedros, J. G., Pennington, C., and McNeil, P. L. 2006. Increased osteogenic response to exercise in metaphyseal versus diaphyseal cortical bone. J.Musculoskelet.Neuronal Interact. 6:258-263.

Hamrick, M. W., Della-Fera, M. A., Choi, Y. H., Pennington, C., Hartzell, D., and Baile, C. A. 2005. Leptin treatment induces loss of bone marrow

adipocytes and increases bone formation in leptin-deficient ob/ob mice. J.Bone Miner.Res. 20:994-1001.

Hang, F., and Barber, A. H. 2010. Nano-mechanical properties of individual mineralized collagen fibrils from bone tissue. J.R.Soc.Interface. 8:500-505.

Hansma, P. K., Fantner, G. E., Kindt, J. H., Thurner, P. J., Schitter, G., Turner, P. J., Udwin, S. F., and Finch, M. M. 2005. Sacrificial bonds in the interfibrillar matrix of bone. J.Musculoskelet.Neuronal Interact. 5:313-315.

Haapasalo, H., Kontulainen, S., Sievänen, H., Kannus, P., Järvinen, M., and Vuori, l. 2000. Exercise-induced bone gain is due to enlargement in bone size without a change in volumetric bone density: a peripheral quantitative computed tomography study of the upper arms of male tennis players. Bone. 27:351-357.

Harris, M., Nguyen, T. V., Howard, G. M., Kelly, P. J., and Eisman, J. A. 1998. Genetic and environmental correlations between bone formation and bone mineral density: a twin study. Bone. 22:141-145.

Hassenkam, T., Jorgensen, H. L., and Lauritzen, J. B. 2006. Mapping the imprint of bone remodeling by atomic force microscopy. Anat.Rec.A.Discov.Mol.Cell.Evol.Biol. 288:1087-1094.

Hassenkam, T., Jorgensen, H. L., Pedersen, M. B., Kourakis, A. H., Simonsen, L., and Lauritzen, J. B. 2005. Atomic force microscopy on human trabecular bone from an old woman with osteoporotic fractures. Micron. 36:681-687.

Hassenkam, T., Fantner, G. E., Cutroni, J. A., Weaver, J. C., Morse, D. E., and Hansma, P. K. 2004. High-resolution AFM imaging of intact and fractured trabecular bone. Bone. 35:4-10.

Hattner, R., Epker, B. N., and Frost, H. M. 1965. Suggested sequential mode of control of changes in cell behaviour in adult bone remodelling. Nature. 206:489-490.

Hauge, E. M., Qvesel, D., Eriksen, E. F., Mosekilde, L., and Melsen, F. 2001. Cancellous bone remodeling occurs in specialized compartments lined by cells expressing osteoblastic markers. J.Bone Miner.Res. 16:1575-1582.

Haupt, B. J., Pelling, A. E., and Horton, M. A. 2006. Integrated confocal and scanning probe microscopy for biomedical research. ScientificWorldJournal. 6:1609-1618.

Havill, L. M., Mahaney, M. C., L Binkley, T., and Specker, B. L. 2007. Effects of genes, sex, age, and activity on BMC, bone size, and areal and volumetric BMD. J.Bone Miner.Res. 22:737-746.

Heersche, J. N., Bellows, C. G., and Ishida, Y. 1998. The decrease in bone mass associated with aging and menopause. J.Prosthet.Dent. 79:14-16.

Heikkinen, R., Vihriälä, E., Vainionpää, A., Korpelainen, R., and Jämsä, T. 2007. Acceleration slope of exercise-induced impacts is a determinant of changes in bone density. J.Biomech. 40:2967-2974.

Heinonen, A., Sievänen, H., Kyröläinen, H., Perttunen, J., and Kannus, P. 2001. Mineral mass, size, and estimated mechanical strength of triple jumpers' lower limb. Bone. 29:279-285.

Heinonen, A., Sievänen, H., Kannus, P., Oja, P., Pasanen, M., and Vuori, I. 2000. High-impact exercise and bones of growing girls: a 9-month controlled trial. Osteoporos.Int. 11:1010-1017.

Hemayattalab, R. 2010. Effects of physical training and calcium intake on bone mineral density of students with mental retardation. Res.Dev.Disabil. 31:784-789.

Hengsberger, S., Kulik, A., and Zysset, P. 2002. Nanoindentation discriminates the elastic properties of individual human bone lamellae under dry and physiological conditions. Bone. 30:178-184.

Hengsberger, S., Kulik, A., and Zysset, P. 2001. A combined atomic force microscopy and nanoindentation technique to investigate the elastic properties of bone structural units. Eur.Cell.Mater. 1:12-17.

Henriksen, K., Neutzsky-Wulff, A. V., Bonewald, L. F., and Karsdal, M. A. 2009. Local communication on and within bone controls bone remodeling. Bone. 44:1026-1033.

Hernandez, C. J., Beaupre, G. S., Keller, T. S., and Carter, D. R. 2001. The influence of bone volume fraction and ash fraction on bone strength and modulus. Bone. 29:74-78.

Hildebrand, T., Laib, A., Muller, R., Dequeker, J., and Ruegsegger, P. 1999. Direct three-dimensional morphometric analysis of human cancellous bone: microstructural data from spine, femur, iliac crest, and calcaneus. J.Bone Miner.Res. 14:1167-1174.

Hofman, T., Raum, K., Leguerney, I., Saied, A., Peyrin, F., Vico, L., and Laugier, P. 2006. Assessment of bone structure and acoustic impedance in C3H and BL6 mice using high resolution scanning acoustic microscopy. Ultrasonics. 44 Suppl 1:e1307-1311.

Holguin, N., Muir, J., Rubin, C., and Judex, S. 2009. Short applications of very low-magnitude vibrations attenuate expansion of the intervertebral disc during extended bed rest. Spine J. 9:470-477.

Howard, G. M., Nguyen, T. V., Harris, M., Kelly, P. J., and Eisman, J. A. 1998. Genetic and environmental contributions to the association between quantitative ultrasound and bone mineral density measurements: a twin study. J.Bone Miner.Res. 13:1318-1327.

Hubal, M. J., Ingalls, C. P., Allen, M. R., Wenke, J. C., Hogan, H. A., and Bloomfield, S. A. 2005. Effects of eccentric exercise training on cortical bone and muscle strength in the estrogen-deficient mouse. J.Appl.Physiol. 98:1674-1681.

Huddleston, A. L., Rockwell, D., Kulund, D. N., and Harrison, R. B. 1980. Bone mass in lifetime tennis athletes. JAMA. 244:1107-1109.

Hunter, D. J., de Lange, M., Andrew, T., Snieder, H., MacGregor, A. J., and Spector, T. D. 2001. Genetic variation in bone mineral density and calcaneal ultrasound: a study of the influence of menopause using female twins. Osteoporos.Int. 12:406-411.

Hydock, D. S., Iwaniec, U. T., Turner, R. T., Lien, C. Y., Jensen, B. T., Parry, T. L., Schneider, C. M., and Hayward, R. 2008. Effects of voluntary wheel

running on goserelin acetate-induced bone degeneration. Pathophysiology. 15:253-259.

Ilich, J. Z., and Brownbill, R. A. 2008. Habitual and low-impact activities are associated with better bone outcomes and lower body fat in older women. Calcif.Tissue Int. 83:260-271.

Ionova-Martin, S. S., Do, S. H., Barth, H. D., Szadkowska, M., Porter, A. E., Ager, J. W.,3rd, Ager, J. W.,Jr, Alliston, T., Vaisse, C., and Ritchie, R. O. 2010. Reduced size-independent mechanical properties of cortical bone in high-fat diet-induced obesity. Bone. 46:217-225.

Ishikawa, T., and Sakuraba, K. 2009. Biochemical markers of bone turnover. New aspect. Bone metabolism movement in various sports and physical activities. Clin.Calcium. 19:1125-1131.

Ito, M., Nishida, A., Koga, A., Ikeda, S., Shiraishi, A., Uetani, M., Hayashi, K., and Nakamura, T. 2002. Contribution of trabecular and cortical components to the mechanical properties of bone and their regulating parameters. Bone. 31:351-358.

Iwamoto, J., Takeda, T., and Sato, Y. 2005. Effect of treadmill exercise on bone mass in female rats. Exp.Anim. 54:1-6.

Iwamoto, J., Takeda, T., Otani, T., and Yabe, Y. 1998. Age-related changes in cortical bone in women: metacarpal bone mass measurement study. J.Orthop.Sci. 3:90-94.

Iwaniec, U. T., Dube, M. G., Boghossian, S., Song, H., Helferich, W. G., Turner, R. T., and Kalra, S. P. 2009. Body mass influences cortical bone mass independent of leptin signaling. Bone. 44:404-412.

Jämsä, T., Vainionpää, A., Korpelainen, R., Vihriälä, E., and Leppäluoto, J. 2006. Effect of daily physical activity on proximal femur. Clin.Biomech.(Bristol, Avon). 21:1-7.

Janicka, A., Wren, T. A., Sanchez, M. M., Dorey, F., Kim, P. S., Mittelman, S. D., and Gilsanz, V. 2007. Fat mass is not beneficial to bone in adolescents and young adults. J.Clin.Endocrinol.Metab. 92:143-147.

Janz, K. F., Letuchy, E. M., Eichenberger Gilmore, J. M., Burns, T. L., Torner, J. C., Willing, M. C., and Levy, S. M. 2010. Early physical activity provides sustained bone health benefits later in childhood. Med.Sci.Sports Exerc. 42:1072-1078.

Järvinen, M., and Kannus, P. 1997. Injury of an extremity as a risk factor of the development of osteoporosis. J.Bone.Joint.Surg.Am. 79:263-276.

Järvinen, T. L., Sievänen, H., Jokihaara, J., and Einhorn, T. A. 2005. Revival of bone strength: The bottom line. J. Bone.Miner.Res. 20:712-720.

Javaid, M. K., and Cooper, C. 2002. Prenatal and childhood influences on osteoporosis. Best.Pract.Res.Clin.Endocrinol.Metab. 16:349-367.

Jebb, S. A., and Moore, M. S. 1999. Contribution of a sedentary lifestyle and inactivity to the etiology of overweight and obesity: current evidence and research issues. Med.Sci.Sports Exerc. 31:S534-541.

Jee, W. S. 2000. Principles in bone physiology. J.Musculoskelet.Neuronal Interact. 1:11-13.

Jee, W. S. 2001. Bone mechanics handbook, Ed. Cowin, S C, (CRC Press, Boca Raton, 2001), p.5.

Jenkins, M. R., and Denison, A. V. 2008. Smoking status as a predictor of hip fracture risk in postmenopausal women of northwest Texas. Prev.Chronic Dis. 5:A09.

Jian, W. X., Long, J. R., Li, M. X., Liu, X. H., and Deng, H. W. 2005. Genetic determination of variation and covariation of bone mineral density at the hip and spine in a Chinese population. J.Bone Miner.Metab. 23:181-185.

Jiang, Y., Zhao, J., White, D. L., and Genant, H. K. 2000. Micro CT and Micro MR imaging of 3D architecture of animal skeleton. J.Musculoskelet.Neuronal Interact. 1:45-51.

Johnson, M. L., Lara, N., and Kamel, M. A. 2009. How genomics has informed our understanding of the pathogenesis of osteoporosis. Genome Med. 1:84.

Jones, G., and Nguyen, T. V. 2000. Associations between maternal peak bone mass and bone mass in prepubertal male and female children. J.Bone Miner.Res. 15:1998-2004.

Jones, H. H., Priest, J. D., Hayes, W. C., Tichenor, C. C., and Nagel, D. A. 1977. Humeral hypertrophy in response to exercise. J.Bone Joint Surg.Am. 59:204-208.

Judex, S., and Carlson, K. J. 2009. Is bone's response to mechanical signals dominated by gravitational loading? Med.Sci.Sports Exerc. 41:2037-2043.

Juzwiak, C. R., Amancio, O. M., Vitalle, M. S., Szejnfeld, V. L., and Pinheiro, M. M. 2008. Effect of calcium intake, tennis playing, and body composition on bone-mineral density of Brazilian male adolescents. Int.J.Sport Nutr.Exerc.Metab. 18:524-538.

Kadam, N., Khadilkar, A., Chiplonkar, S., Khadilkar, V., and Mughal, Z. 2009. Variation in lumbar spine bone mineral content by age and gender in apparently healthy Indians. J.Bone Miner.Metab. 27:705-712.

Kadow-Romacker, A., Hoffmann, J. E., Duda, G., Wildemann, B., and Schmidmaier, G. 2009. Effect of mechanical stimulation on osteoblast- and osteoclast-like cells *in vitro*. Cells Tissues Organs. 190:61-68.

Kalu, D. N., Banu, J., and Wang, L. 2000. How cancellous and cortical bones adapt to loading and growth hormone. J.Musculoskelet.Neuronal Interact. 1:19-23.

Kannus, P., Haapasalo, H., Sievänen, H., Oja, P., and Vuori, I. 1994. The site-specific effects of long-term unilateral activity on bone mineral density and content. Bone. 15:279-284.

Kannus, P., Haapasalo, H., Sankelo, M., Sievänen, H., Pssanen, M., Heinonen, A., Oja, P., and Vuori, I. 1995. Effect of starting age of physical actvity on bone mass in the dominant arm of tennis and squash players. Ann.Intern.Med. 123:27-31.

Kannus, P., Sievänen, H., Palvanen, M., Järvinen, T., and Parkkari, J. 2005. Prevention of falls and consequent injuries in elderly people. Lancet. 366:1885-1893.

Karlsson, M. K., Nordqvist, A., and Karlsson, C. 2008. Sustainability of exercise-induced increases in bone density and skeletal structure. Food.Nutr.Res. 52:10.3402/fnr.v52i0.1872. Epub 2008 Oct 1.

Kartsogiannis, V., and Ng, K. W. 2004. Cell lines and primary cell cultures in the study of bone cell biology. Mol.Cell.Endocrinol. 228:79-102.

Kaufman, J. M., Ostertag, A., Saint-Pierre, A., Cohen-Solal, M., Boland, A., Van Pottelbergh, I., Toye, K., de Vernejoul, M. C., and Martinez, M. 2008. Genome-wide linkage screen of bone mineral density (BMD) in European pedigrees ascertained through a male relative with low BMD values: evidence for quantitative trait loci on 17q21-23, 11q12-13, 13q12-14, and 22q11. J.Clin.Endocrinol.Metab. 93:3755-3762.

Kelly, S. A., Czech, P. P., Wight, J. T., Blank, K. M., and Garland, T.,Jr. 2006. Experimental evolution and phenotypic plasticity of hindlimb bones in high-activity house mice. J.Morphol. 267:360-374.

Kennedy, O. D., Brennan, O., Mauer, P., Rackard, S. M., O'Brien, F. J., Taylor, D., and Lee, T. C. 2008. The effects of increased intracortical remodeling on microcrack behaviour in compact bone. Bone. 43:889-893.

Keogh, J. W., Kilding, A., Pidgeon, P., Ashley, L., and Gillis, D. 2009. Physical benefits of dancing for healthy older adults: a review. J.Aging Phys.Act. 17:479-500.

Kerr, D., Morton, A., Dick, I., and Prince, R. 1996. Exercise effects on bone mass in postmenopausal women are site-specific and load-dependent. J.Bone Miner.Res. 11:218-225.

Kettunen, J. A., Impivaara, O., Kujala, U. M., Linna, M., Maki, J., Raty, H., Alanen, E., Kaprio, J., Videman, T., and Sarna, S. 2010. Hip fractures and femoral bone mineral density in male former elite athletes. Bone. 46:330-335.

Khosla, S., Riggs, B. L., Atkinson, E. J., Oberg, A. L., McDaniel, L. J., Holets, M., Peterson, J. M., and Melton, L. J.,3rd. 2006. Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive *in vivo* assessment. J.Bone Miner.Res. 21:124-131.

Kiel, D. P., Demissie, S., Dupuis, J., Lunetta, K. L., Murabito, J. M., and Karasik, D. 2007. Genome-wide association with bone mass and geometry in the Framingham Heart Study. BMC Med.Genet. 8 Suppl 1:S14.

Kingsmill, V. J., Gray, C. M., Moles, D. R., and Boyde, A. 2007. Cortical vascular canals in human mandible and other bones. J.Dent.Res. 86:368-372.

Kinney, J. H. 1999. Connectivity and the elastic properties of cancellous bone. Bone. 25:741-742.

Kirmani, S., Christen, D., van Lenthe, G. H., Fischer, P. R., Bouxsein, M. L., McCready, L. K., Melton, L. J.,3rd, Riggs, B. L., Amin, S., Muller, R., and Khosla, S. 2009. Bone structure at the distal radius during adolescent growth. J.Bone Miner.Res. 24:1033-1042.

Kitagawa, J., and Nakahara, Y. 2008. Associations of daily walking steps with calcaneal ultrasound parameters and a bone resorption marker in elderly Japanese women. J.Physiol.Anthropol. 27:295-300.

Klein, R. F. 2002. Genetic regulation of bone mineral density in mice. J.Musculoskelet.Neuronal Interact. 2:232-236.

Knobloch, K., Schreibmueller, L., Jagodzinski, M., Zeichen, J., and Krettek, C. 2007. Rapid rehabilitation programme following sacral stress fracture in a long-distance running female athlete. Arch.Orthop.Trauma.Surg. 127:809-813.

Koerner, A., Kratzsch, J., and Kiess, W. 2005. Adipocytokines: leptin--the classical, resistin--the controversical, adiponectin--the promising, and more to come. Best Pract.Res.Clin.Endocrinol.Metab. 19:525-546.

Kohrt, W. M., Barry, D. W., and Schwartz, R. S. 2009. Muscle forces or gravity: what predominates mechanical loading on bone? Med.Sci.Sports Exerc. 41:2050-2055.

Kontulainen, S., Heinonen, A., Kannus, P., Pasanen, M., Sievänen, H., and Vuori, I. 2004. Former exercisers of an 18-month intervention display residual aBMD benefits compared with control women 3.5 years post-intervention: a follow-up of a randomized controlled high-impact trial. Osteoporos.Int. 15:248-251.

Kontulainen, S., Sievänen, H., Kannus, P., Pasanen, M., and Vuori, I. 2002. Effect of long-term impact-loading on mass, size, and estimated strength of humerus and radius of female racquet-sports players: a peripheral quantitative computed tomography study between young and old starters and controls. J.Bone Miner.Res. 17:2281-2289.

Kontulainen, S. A., Johnston, J. D., Liu, D., Leung, C., Oxland, T. R., and McKay, H. A. 2008. Strength indices from pQCT imaging predict up to 85% of variance in bone failure properties at tibial epiphysis and diaphysis. J.Musculoskelet.Neuronal Interact. 8:401-409.

Kontulainen, S., Kannus, P., Haapasalo, H., Heinonen, A., Sievänen, H., Oja, P., and Vuori, I. 1999. Changes in bone mineral content with decreased training in competitive young adult tennis players and controls: a prospective 4-yr follow-up. Med.Sci.Sports Exerc. 31:646-652.

Kubicek, V., and Lukes, I. 2010. Bone-seeking probes for optical and magnetic resonance imaging. Future.Med.Chem. 2:521-531.

Kukuljan, S., Nowson, C. A., Bass, S. L., Sanders, K., Nicholson, G. C., Seibel, M. J., Salmon, J., and Daly, R. M. 2009. Effects of a multi-component exercise program and calcium-vitamin-D3-fortified milk on bone mineral density in older men: a randomised controlled trial. Osteoporos.Int. 20:1241-1251.

Kuo, C. W., Chang, T. H., Chi, W. L., and Chu, T. C. 2008. Effect of cigarette smoking on bone mineral density in healthy Taiwanese middle-aged men. J.Clin.Densitom. 11:518-524.

Kyung, T. W., Lee, J. E., Van Phan, T., Yu, R., and Choi, H. S. 2009. Osteoclastogenesis by bone marrow-derived macrophages is enhanced in obese mice. J.Nutr. 139:502-506.

Laib, A., Kumer, J. L., Majumdar, S., and Lane, N. E. 2001. The temporal changes of trabecular architecture in ovariectomized rats assessed by MicroCT. Osteoporos.Int. 12:936-941.

Laib, A., Barou, O., Vico, L., Lafage-Proust, M. H., Alexandre, C., and Rugsegger, P. 2000. 3D micro-computed tomography of trabecular and cortical bone architecture with application to a rat model of immobilisation osteoporosis. Med.Biol.Eng.Comput. 38:326-332.

Lane, N. E., and Yao, W. 2009. Developments in the scientific understanding of osteoporosis. Arthritis Res.Ther. 11:228.

Lange, M., Qvortrup, K., Svendsen, O. L., Flyvbjerg, A., Nowak, J., Petersen, M. M., OLgaard, K., and Feldt-Rasmussen, U. 2004. Abnormal bone collagen morphology and decreased bone strength in growth hormone-deficient rats. Bone. 35:178-185.

Lanyon, L. E. 1992. Control of bone architecture by functional load bearing. J.Bone Miner.Res. 7:S369-375.

Lanyon, L. E. 1993. Osteocytes, strain detection, bone modeling and remodeling. Calcif.Tissue Int. 53 Suppl 1:S102-6; discussion S106-7.

Lapauw, B. M., Taes, Y., Bogaert, V., Vanbillemont, G., Goemaere, S., Zmierczak, H. G., De Bacquer, D., and Kaufman, J. M. 2009. Serum estradiol is associated with volumetric BMD and modulates the impact of physical activity on bone size at the age of peak bone mass: a study in healthy male siblings. J.Bone Miner.Res. 24:1075-1085.

Laval-Jeantet, A. M., Bergot, C., Carroll, R., and Garcia-Schaefer, F. 1983. Cortical bone senescence and mineral bone density of the humerus. Calcif.Tissue Int. 35:268-272.

Lazenby, R. A. 1990. Continuing periosteal apposition. II: The significance of peak bone mass, strain equilibrium, and age-related activity differentials for mechanical compensation in human tubular bones. Am.J.Phys.Anthropol. 82:473-484.

Lee, N. K., Sowa, H., Hinoi, E., Ferron, M., Ahn, J. D., Confavreux, C., Dacquin, R., Mee, P. J., McKee, M. D., Jung, D. Y., Zhang, Z., Kim, J. K., Mauvais-Jarvis, F., Ducy, P., and Karsenty, G. 2007. Endocrine regulation of energy metabolism by the skeleton. Cell. 130:456-469.

Lehenkari, P. P., Charras, G. T., Nykanen, A., and Horton, M. A. 2000. Adapting atomic force microscopy for cell biology. Ultramicroscopy. 82:289-295.

Lehtonen-Veromaa, M., Mottonen, T., Nuotio, I., Heinonen, O. J., and Viikari, J. 2000a. Influence of physical activity on ultrasound and dual-energy X-ray absorptiometry bone measurements in peripubertal girls: a cross-sectional study. Calcif.Tissue Int. 66:248-254.

Lehtonen-Veromaa, M., Mottonen, T., Svedstrom, E., Hakola, P., Heinonen, O. J., and Viikari, J. 2000b. Physical activity and bone mineral acquisition in peripubertal girls. Scand.J.Med.Sci.Sports. 10:236-243.

Leibowitz, S. F., Chang, G. Q., Dourmashkin, J. T., Yun, R., Julien, C., and Pamy, P. P. 2006. Leptin secretion after a high-fat meal in normal-weight rats: strong predictor of long-term body fat accrual on a high-fat diet. Am.J.Physiol.Endocrinol.Metab. 290:e258-67.

Leite, M., Padrao, P., and Moreira, P. 2007. Nutritional intake and bone mineral density in female adolescents. Acta Med.Port. 20:299-306.

Lenchik, L., Hsu, F. C., Register, T. C., Lohman, K. K., Freedman, B. I., Langefeld, C. D., Bowden, D. W., and Carr, J. J. 2004. Heritability of spinal trabecular volumetric bone mineral density measured by QCT in the Diabetes Heart Study. Calcif.Tissue Int. 75:305-312.

Leonard, M. B., Shults, J., Wilson, B. A., Tershakovec, A. M., and Zemel, B. S. 2004. Obesity during childhood and adolescence augments bone mass and bone dimensions. Am.J.Clin.Nutr. 80:514-523.

Leppänen, O. V., Sievänen, H., Jokihaara, J., Pajamaki, I., Kannus, P., and Järvinen, T. L. 2008. Pathoenesis of age-related osteoporosis: impaired mechano-responsiveness of bone is not the culprit. Plose.One. 3:e2540.

Lestkinen, T., Waller, K., Mutikainen, S., Aaltonen, S., Ronkainen, P. H., Alen, M., Sipilä, S., Kovanen, V., Perhonen, M., Pietiläinen, K. H., Cheng, S., Suominen, H., Kainulainen, H., Kaprio, J., and Kujala, U. M. 2009. Effects of 32-year leisure time physical activity discordance in twin pairs on health (TWINACTIVE study): aims, design and results for physical fitness. Twin.Res.Hum.Genet. 12:108-117.

Letechipia, J. E., Alessi, A., Rodriguez, G., and Asbun, J. 2010. Would increased interstitial fluid flow through in situ mechanical stimulation enhance bone remodeling? Med.Hypotheses. 75:196-198.

Leung, K. S., Lee, K. M., Cheung, W. H., Ng, E. S., and Qin, L. 2004. Characteristics of long bone DXA reference data in Hong Kong Chinese. J.Clin.Densitom. 7:192-200.

Liang, M. T., Arnaud, S. B., Steele, C. R., Hatch, P., and Moreno, A. 2005. Ulnar and tibial bending stiffness as an index of bone strength in synchronized swimmers and gymnasts. Eur.J.Appl.Physiol. 94:400-407.

Lin, Y., and Xu, S. 2010. AFM analysis of the lacunar-canalicular network in demineralized compact bone. J.Microsc. 241:291-302.

Lin, Y. C., Lyle, R. M., Weaver, C. M., McCabe, L. D., McCabe, G. P., Johnston, C. C., and Teegarden, D. 2003. Peak spine and femoral neck bone mass in young women. Bone. 32:546-553.

Linden, C., Ahlborg, H. G., Besjakov, J., Gardsell, P., and Karlsson, M. K. 2006. A school curriculum-based exercise program increases bone mineral accrual and bone size in prepubertal girls: two-year data from the pediatric osteoporosis prevention (POP) study. J.Bone Miner.Res. 21:829-835.

Lindgren, C., Hallman, M., Sennerby, L., and Sammons, R. 2010. Back-scattered electron imaging and elemental analysis of retrieved bone tissue following sinus augmentation with deproteinized bovine bone or biphasic calcium phosphate. Clin.Oral Implants Res. 21:924-930.

Link, T. M., and Bauer, J. S. 2002. Imaging of trabecular bone structure. Semin.Musculoskelet.Radiol. 6:253-261.

Lissett, C. A., and Shalet, S. M. 2000. Effects of growth hormone on bone and muscle. Growth Horm.IGF Res. 10 Suppl B:S95-101.

Liu, L., Maruno, R., Mashimo, T., Sanka, K., Higuchi, T., Hayashi, K., Shirasaki, Y., Mukai, N., Saitoh, S., and Tokuyama, K. 2003. Effects of physical

training on cortical bone at midtibia assessed by peripheral QCT. J.Appl.Physiol. 95:219-224.

Liu, P. Y., Qin, Y. J., Recker, R. R., and Deng, H. W. 2004. Evidence for a major gene underlying bone size variation in the Chinese. Am.J.Hum.Biol. 16:68-77.

Liu-Ambrose, T. Y., Khan, K. M., Eng, J. J., Heinonen, A., and McKay, H. A. 2004. Both resistance and agility training increase cortical bone density in 75- to 85-year-old women with low bone mass: a 6-month randomized controlled trial. J.Clin.Densitom. 7:390-398.

Lochmuller, E. M., Kristin, J., Matsuura, M., Kuhn, V., Hudelmaier, M., Link, T. M., and Eckstein, F. 2008. Measurement of trabecular bone microstructure does not improve prediction of mechanical failure loads at the distal radius compared with bone mass alone. Calcif.Tissue Int. 83:293-299.

Long, J. R., Liu, P. Y., Lu, Y., Xiong, D. H., Zhao, L. J., Zhang, Y. Y., Elze, L., Recker, R. R., and Deng, H. W. 2004. Association between COL1A1 gene polymorphisms and bone size in Caucasians. Eur.J.Hum.Genet. 12:383-388.

Lorentzon, M., Eriksson, A. L., Nilsson, S., Mellstrom, D., and Ohlsson, C. 2007a. Association between physical activity and BMD in young men is modulated by catechol-O-methyltransferase (COMT) genotype: the GOOD study. J.Bone Miner.Res. 22:1165-1172.

Lorentzon, M., Mellstrom, D., Haug, E., and Ohlsson, C. 2007b. Smoking is associated with lower bone mineral density and reduced cortical thickness in young men. J.Clin.Endocrinol.Metab. 92:497-503.

Lorentzon, M., Mellstrom, D., and Ohlsson, C. 2005. Association of amount of physical activity with cortical bone size and trabecular volumetric BMD in young adult men: the GOOD study. J.Bone Miner.Res. 20:1936-1943.

Lui, P. P., Qin, L., and Chan, K. M. 2008. Tai Chi Chuan exercises in enhancing bone mineral density in active seniors. Clin.Sports Med. 27:75-86.

Luu, Y. K., Capilla, E., Rosen, C. J., Gilsanz, V., Pessin, J. E., Judex, S., and Rubin, C. T. 2009. Mechanical stimulation of mesenchymal stem cell proliferation and differentiation promotes osteogenesis while preventing dietary-induced obesity. J.Bone Miner.Res. 24:50-61.

Lynch, N. A., Ryan, A. S., Evans, J., Katzel, L. I., and Goldberg, A. P. 2007. Older elite football players have reduced cardiac and osteoporosis risk factors. Med.Sci.Sports Exerc. 39:1124-1130.

Macdonald, H. M., Nishiyama, K. K., Kang, J., Hanley, D. A., and Boyd, S. K. 2010. Age-related patterns of trabecular and cortical bone loss differ between sexes and skeletal sites: A population-based HR-pQCT study. J.Bone Miner.Res. 26:50-62.

Macdonald, H. M., Cooper, D. M., and McKay, H. A. 2009. Anterior-posterior bending strength at the tibial shaft increases with physical activity in boys: evidence for non-uniform geometric adaptation. Osteoporos.Int. 20:61-70.

Macdonald, H. M., Cooper, D. M., and McKay, H. A. 2008a. Anterior-posterior bending strength at the tibial shaft increases with physical activity in boys: evidence for non-uniform geometric adaptation. Osteoporos.Int. 20:61-70.

Macdonald, H. M., Kontulainen, S. A., Petit, M. A., Beck, T. J., Khan, K. M., and McKay, H. A. 2008b. Does a novel school-based physical activity model benefit femoral neck bone strength in pre- and early pubertal children? Osteoporos.Int. 19:1445-1456.

Macdonald, H. M., McGuigan, F. E., Lanham-New, S. A., Fraser, W. D., Ralston, S. H., and Reid, D. M. 2008c. Vitamin K1 intake is associated with higher bone mineral density and reduced bone resorption in early postmenopausal Scottish women: no evidence of gene-nutrient interaction with apolipoprotein E polymorphisms. Am.J.Clin.Nutr. 87:1513-1520.

Macdonald, H. M., Kontulainen, S. A., Khan, K. M., and McKay, H. A. 2007. Is a school-based physical activity intervention effective for increasing tibial bone strength in boys and girls? J.Bone Miner.Res. 22:434-446.

MacKelvie, K. J., Petit, M. A., Khan, K. M., Beck, T. J., and McKay, H. A. 2004. Bone mass and structure are enhanced following a 2-year randomized controlled trial of exercise in prepubertal boys. Bone. 34:755-764.

MacKelvie, K. J., Khan, K. M., Petit, M. A., Janssen, P. A., and McKay, H. A. 2003. A school-based exercise intervention elicits substantial bone health benefits: a 2-year randomized controlled trial in girls. Pediatrics. 112:e447.

Mackelvie, K. J., McKay, H. A., Khan, K. M., and Crocker, P. R. 2001. A school-based exercise intervention augments bone mineral accrual in early pubertal girls. J.Pediatr. 139:501-508.

Mackie, E. J. 2003. Osteoblasts: novel roles in orchestration of skeletal architecture. Int.J.Biochem.Cell Biol. 35:1301-1305.

Magarey, A. M., Boulton, T. J., Chatterton, B. E., Schultz, C., Nordin, B. E., and Cockington, R. A. 1999. Bone growth from 11 to 17 years: relationship to growth, gender and changes with pubertal status including timing of menarche. Acta Paediatr. 88:139-146.

Maimoun, L., Coste, O., Galtier, F., Mura, T., Mariano-Goulart, D., Paris, F., and Sultan, C. 2010. Bone mineral density acquisition in peripubertal female rhythmic gymnasts is directly associated with plasma IGF-1/IGFBP-3 ratio. Eur.J.Endocrinol. 163:157-164.

Maimoun, L., and Sultan, C. 2010. Effects of physical activity on bone remodeling. Metabolism. 60:373-388.

Makovey, J., Nguyen, T. V., Naganathan, V., Wark, J. D., and Sambrook, P. N. 2007. Genetic effects on bone loss in peri- and postmenopausal women: a longitudinal twin study. J.Bone Miner.Res. 22:1773-1780.

Mancini, L., Becherini, L., Benvenuti, S., and Brandi, M. L. 1997. Bioeffects of a nitric oxide donor in a human preosteoclastic cell line. Int.J.Clin.Pharmacol.Res. 17:93-96.

Marcus, R. 1991. Skeletal aging understanding the functional and structural basis of osteoporosis. Trends Endocrinol.Metab. 2:53-58.

Marcus, R., Feldman D., Nelson D., and Rosen C.J. 2009. The bone organ system: form and function, fundamentals of osteoporosis (Academic Press; 1 edition), chapter I: 1-6.

Martin, R. B. 2007. Targeted bone remodeling involves BMU steering as well as activation. Bone. 40:1574-1580.

Martin, R. B. 2003. Fatigue microdamage as an essential element of bone mechanics and biology. Calcif.Tissue Int. 73:101-107.

Martin, R. B., and Burr, D. B. 1984. Non-invasive measurement of long bone cross-sectional moment of inertia by photon absorptiometry. J.Biomech. 17:195-201.

Martyn-St James, M., and Carroll, S. 2006. Progressive high-intensity resistance training and bone mineral density changes among premenopausal women: evidence of discordant site-specific skeletal effects. Sports Med. 36:683-704.

Mashiba, T., Hirano, T., Turner, C. H., Forwood, M. R., Johnston, C. C., and Burr, D. B. 2000. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J.Bone Miner.Res. 15:613-620.

Markovic, V., Jelic, T., Wardlaw, G. M., Ilich, J. Z., Goel, P. K., Wright, J. K., Andon, M. B., Smith, K. T., and Heaney, R. P. 1994. Timing of peak bone mass in Caucasian females and its implication for the prevention of osteoporosis. Inference from a cross-sectional model. J.Clin.Invest. 93:799-808.

Matthews, B. L., Bennell, K. L., McKay, H. A., Khan, K. M., Baxter-Jones, A. D., Mirwald, R. L., and Wark, J. D. 2006. Dancing for bone health: a 3-year longitudinal study of bone mineral accrual across puberty in female non-elite dancers and controls. Osteoporos.Int. 17:1043-1054.

McCalden, R. W., McGeough, J. A., Barker, M. B., and Court-Brown, C. M. 1993. Age-related changes in the tensile properties of cortical bone. The relative importance of changes in porosity, mineralization, and microstructure. J.Bone Joint Surg.Am. 75:1193-1205.

McKay, H., Liu, D., Egeli, D., Boyd, S., and Burrows, M. 2011. Physical activity positively predicts bone architecture and bone strength in adolescent males and females. Acta Paediatr. 100:97-101.

Mezuk, B., Eaton, W. W., Golden, S. H., Wand, G., and Lee, H. B. 2008. Depression, antidepressants, and bone mineral density in a population-based cohort. J.Gerontol.A Biol.Sci.Med.Sci. 63:1410-1415.

Michaelsson, K., Olofsson, H., Jensevik, K., Larsson, S., Mallmin, H., Berglund, L., Vessby, B., and Melhus, H. 2007. Leisure physical activity and the risk of fracture in men. PLoS Med. 4:e199.

Middleton, K. M., Shubin, C. E., Moore, D. C., Carter, P. A., Garland, T.,Jr, and Swartz, S. M. 2008. The relative importance of genetics and phenotypic plasticity in dictating bone morphology and mechanics in aged mice: evidence from an artificial selection experiment. Zoology (Jena). 111:135-147.

Middleton, K. M., Goldstein, B. D., Guduru, P. R., Waters, J. F., Kelly, S. A., Swartz, S. M., and Garland, T.,Jr. 2010. Variation in within-bone stiffness measured by nanoindentation in mice bred for high levels of voluntary wheel running. J.Anat. 216:121-131.

Miggiano, G. A., and Gagliardi, L. 2005. Diet, nutrition and bone health. Clin.Ter. 156:47-56.

Mikkola, T., Sipilä, S., Portegijs, E., Kallinen, M., Alen, M., Kiviranta, I., Pekkonen, M., and Heinonen, A. 2007. Impaired geometric properties of tibia in older women with hip fracture history. Osteoporos.Int. 18:1083-1090.

Mikkola, T. M., Sipilä, S., Rantanen, T., Sievänen, H., Suominen, H., Kaprio, J., Koskenvuo, M., Kauppinen, M., and Heinonen, A. 2008. Genetic and environmental influence on structural strength of weight-bearing and non-weight-bearing bone: a twin study. J.Bone Miner.Res. 23:492-498.

Mikkola, T. M., Heinonen, A., Kovanen, V., Cheng, S., Kujala, U. M., Suominen, H., Alen, M., Puolakka, J., Ankarberg-Lindgren, C., Ronkainen, P. H., Koskenvuo, M., Koskenvuo, M., Kaprio, J., Rantanen, T. and Sipilä, S. 2011. Influence of long-term postmenopausal hormone-replacement therapy on estimated structural bone strength: a study in discordant monozygotic twins. J.Bone Miner.Res. 26:546-552.

Miller, L. E., Wootten, D. F., Nickols-Richardson, S. M., Ramp, W. K., Steele, C. R., Cotton, J. R., Carneal, J. P., and Herbert, W. G. 2007. Isokinetic training increases ulnar bending stiffness and bone mineral in young women. Bone. 41:685-689.

Mkukuma, L. D., Skakle, J. M., Gibson, I. R., Imrie, C. T., Aspden, R. M., and Hukins, D. W. 2004. Effect of the proportion of organic material in bone on thermal decomposition of bone mineral: an investigation of a variety of bones from different species using thermogravimetric analysis coupled to mass spectrometry, high-temperature X-ray diffraction, and Fourier transform infrared spectroscopy. Calcif.Tissue Int. 75:321-328.

Modlesky, C. M., Majumdar, S., and Dudley, G. A. 2008. Trabecular bone microarchitecture in female collegiate gymnasts. Osteoporos.Int. 19:1011-1018.

Moisio, K. C., Podolskaya, G., Barnhart, B., Berzins, A., and Sumner, D. R. 2003. pQCT provides better prediction of canine femur breaking load than does DXA. J.Musculoskelet.Neuronal Interact. 3:240-245.

Morenko, B. J., Bove, S. E., Chen, L., Guzman, R. E., Juneau, P., Bocan, T. M., Peter, G. K., Arora, R., and Kilgore, K. S. 2004. *In vivo* micro computed tomography of subchondral bone in the rat after intra-articular administration of monosodium iodoacetate. Contemp.Top.Lab.Anim.Sci. 43:39-43.

Mori, T., Okimoto, N., Sakai, A., Okazaki, Y., Nakura, N., Notomi, T., and Nakamura, T. 2003. Climbing exercise increases bone mass and trabecular bone turnover through transient regulation of marrow osteogenic and osteoclastogenic potentials in mice. J.Bone Miner.Res. 18:2002-2009.

Morseth, B., Emaus, N., Wilsgaard, T., Jacobsen, B. K., and Jorgensen, L. 2010. Leisure time physical activity in adulthood is positively associated with bone mineral density 22 years later. The Tromso study. Eur.J.Epidemiol. 25:325-331.

Moyer-Mileur, L. J., Xie, B., Ball, S. D., and Pratt, T. 2003. Bone mass and density response to a 12-month trial of calcium and vitamin D supplement in preadolescent girls. J.Musculoskelet.Neuronal Interact. 3:63-70.

Mullins, L. P., Bruzzi, M. S., and McHugh, P. E. 2007. Measurement of the microstructural fracture toughness of cortical bone using indentation fracture. J.Biomech. 40:3285-3288.

Murphy, N. M., and Carroll, P. 2003. The effect of physical activity and its interaction with nutrition on bone health. Proc.Nutr.Soc. 62:829-838.

Murray, P. D., and Huxley, J. S. 1925. Self-differentiation in the grafted limb-bud of the chick. J.Anat. 59:379-384.

Nagaraja, S., Couse, T. L., and Guldberg, R. E. 2005. Trabecular bone microdamage and microstructural stresses under uniaxial compression. J.Biomech. 38:707-716.

Nagasawa, S., Honda, A., Sogo, N., and Umemura, Y. 2008. Effects of low-repetition jump exercise on osteogenic response in rats. J.Bone Miner.Metab. 26:226-230.

Nakamura, K., Saito, T., Oyama, M., Oshiki, R., Kobayashi, R., Nishiwaki, T., Nashimoto, M., and Tsuchiya, Y. 2010. Vitamin D sufficiency is associated with low incidence of limb and vertebral fractures in community-dwelling elderly Japanese women: the Muramatsu Study. Osteoporos.Int. 22:97-103.

Nalla, R. K., Porter, A. E., Daraio, C., Minor, A. M., Radmilovic, V., Stach, E. A., Tomsia, A. P., and Ritchie, R. O. 2005. Ultrastructural examination of dentin using focused ion-beam cross-sectioning and transmission electron microscopy. Micron. 36:672-680.

Nara-Ashizawa, N., Liu, L. J., Higuchi, T., Tokuyama, K., Hayashi, K., Shirasaki, Y., Amagai, H., and Saitoh, S. 2002. Paradoxical adaptation of mature radius to unilateral use in tennis playing. Bone. 30:619-623.

Nazarian, A., Muller, J., Zurakowski, D., Muller, R., and Snyder, B. D. 2007. Densitometric, morphometric and mechanical distributions in the human proximal femur. J.Biomech. 40:2573-2579.

Nemet, D., Berger-Shemesh, E., Wolach, B., and Eliakim, A. 2006. A combined dietary-physical activity intervention affects bone strength in obese children and adolescents. Int.J.Sports Med. 27:666-671.

Newhall, K. M., Rodnick, K. J., van der Meulen, M. C., Carter, D. R., and Marcus, R. 1991. Effects of voluntary exercise on bone mineral content in rats. J.Bone Miner.Res. 6:289-296.

Nguyen, T. V., Howard, G. M., Kelly, P. J., and Eisman, J. A. 1998. Bone mass, lean mass, and fat mass: same genes or same environments? Am.J.Epidemiol. 147:3-16.

Niehoff, A., Kersting, U. G., Zaucke, F., Morlock, M. M., and Bruggemann, G. P. 2004. Adaptation of mechanical, morphological, and biochemical properties of the rat growth plate to dose-dependent voluntary exercise. Bone. 35:899-908.

Nikander, R., Sievänen, H., Uusi-Rasi, K., Heinonen, A., and Kannus, P. 2006. Loading modalities and bone structures at nonweight-bearing upper

extremity and weight-bearing lower extremity: a pQCT study of adult female athletes. Bone. 39:886-894.

Nikander, R., Sievänen, H., Heinonen, A., and Kannus, P. 2005. Femoral neck structure in adult female athletes subjected to different loading modalities. J.Bone Miner.Res. 20:520-528.

Nikander, R., Sievänen, H., Heinonen, A., Daly, R. M., Uusi-Rasi, K., and Kannus, P. 2010. Targeted exercise against osteoporosis: A systemic review and meta-analysis fro optimising bone strength throughout life. BMC.Med. 8:e47.

Nikander, R., Gagnon, C., Dunstan, D. W., Magliano, D. J., Ebeling, P. R., Lu, Z. X., Zimmet, P. Z., Shaw, J. E., and Daly, R. M. 2011. Frequent walking, but not total physical activity, is associated with increased fracture incidence: A 5-year follow-up of an Australian population-based prospective study (AusDiab). J.Bone Miner.Res. 26:1638-1647.

Nilsson, M., Ohlsson, C., Sundh, D., Mellstrom, D., and Lorentzon, M. 2010. Association of physical activity with trabecular microstructure and cortical bone at distal tibia and radius in young adult men. J.Clin.Endocrinol.Metab. 95:2917-2926.

Nilsson, M., Ohlsson, C., Mellstrom, D., and Lorentzon, M. 2009. Previous sport activity during childhood and adolescence is associated with increased cortical bone size in young adult men. J.Bone Miner.Res. 24:125-133.

Nilsson, M., Ohlsson, C., Eriksson, A. L., Frandin, K., Karlsson, M., Ljunggren, O., Mellstrom, D., and Lorentzon, M. 2008. Competitive physical activity early in life is associated with bone mineral density in elderly Swedish men. Osteoporos.Int. 19:1557-1566.

Nishiyama, K. K., Macdonald, H. M., Buie, H. R., Hanley, D. A., and Boyd, S. K. 2009. Postmenopausal women with osteopenia have higher cortical porosity and thinner cortices at the distal radius and tibia than women with normal aBMD: An *In Vivo* HR-pQCT Study. J.Bone Miner.Res. 25:882-890.

Noble, B. S. 2008. The osteocyte lineage. Arch.Biochem.Biophys. 473:106-111.

Noda, M., and Rodan, G. A. 1989. Type beta transforming growth factor regulates expression of genes encoding bone matrix proteins. Connect.Tissue Res. 21:71-75.

Nordstrom, A., Olsson, T., and Nordstrom, P. 2006. Sustained benefits from previous physical activity on bone mineral density in males. J.Clin.Endocrinol.Metab. 91:2600-2604.

Nordstrom, P., and Lorentzon, R. 1999. Influence of heredity and environment on bone density in adolescent boys: a parent-offspring study. Osteoporos.Int. 10:271-277.

Nordstrom, S. M., Carleton, S. M., Carson, W. L., Eren, M., Phillips, C. L., and Vaughan, D. E. 2007. Transgenic over-expression of plasminogen activator inhibitor-1 results in age-dependent and gender-specific increases in bone strength and mineralization. Bone. 41:995-1004.

Norman, J., Shapter, J. G., Short, K., Smith, L. J., and Fazzalari, N. L. 2008. Micromechanical properties of human trabecular bone: a hierarchical investigation using nanoindentation. J.Biomed.Mater.Res.A. 87:196-202.

Norman, T. L., Yeni, Y. N., Brown, C. U., and Wang, Z. 1998. Influence of microdamage on fracture toughness of the human femur and tibia. Bone. 23:303-306.

Nowak, A., Stemplewski, R., Szeklicki, R., Karolkiewicz, J., Pilaczynska-Szczesniak, L., and Osinski, W. 2005. Biochemical markers of bone metabolism in healthy elderly men. The relationship to physical activity. Aging Male. 8:75-80.

Nurmi-Lawton, J. A., Baxter-Jones, A. D., Mirwald, R. L., Bishop, J. A., Taylor, P., Cooper, C., and New, S. A. 2004. Evidence of sustained skeletal benefits from impact-loading exercise in young females: a 3-year longitudinal study. J.Bone Miner.Res. 19:314-322.

Nyman, J. S., Ni, Q., Nicolella, D. P., and Wang, X. 2008. Measurements of mobile and bound water by nuclear magnetic resonance correlate with mechanical properties of bone. Bone. 42:193-199.

Nyman, J. S., Roy, A., Shen, X., Acuna, R. L., Tyler, J. H., and Wang, X. 2006. The influence of water removal on the strength and toughness of cortical bone. J.Biomech. 39:931-938.

Nyman, J. S., Reyes, M., and Wang, X. 2005. Effect of ultrastructural changes on the toughness of bone. Micron. 36:566-582.

Nyssen-Behets, C., Duchesne, P. Y., and Dhem, A. 1997. Structural changes with aging in cortical bone of the human tibia. Gerontology. 43:316-325.

O'brien, F. J., Hardiman, D. A., Hazenberg, J. G., Mercy, M. V., Mohsin, S., Taylor, D., and Lee, T. C. 2005. The behaviour of microcracks in compact bone. Eur.J.Morphol. 42:71-79.

Ocarino, N. M., Marubayashi, U., Cardoso, T. G., Guimaraes, C. V., Silva, A. E., Torres, R. C., and Serakides, R. 2007. Physical activity in osteopenia treatment improved the mass of bones directly and indirectly submitted to mechanical impact. J.Musculoskelet.Neuronal Interact. 7:84-93.

Ophoff, J., Callewaert, F., Venken, K., De Gendt, K., Ohlsson, C., Gayan-Ramirez, G., Decramer, M., Boonen, S., Bouillon, R., Verhoeven, G., and Vanderschueren, D. 2009. Physical activity in the androgen receptor knockout mouse: evidence for reversal of androgen deficiency on cancellous bone. Biochem.Biophys.Res.Commun. 378:139-144.

Orito, S., Kuroda, T., Onoe, Y., Sato, Y., and Ohta, H. 2009. Age-related distribution of bone and skeletal parameters in 1,322 Japanese young women. J.Bone Miner.Metab. 27:698-704.

Palombaro, K. M. 2005. Effects of walking-only interventions on bone mineral density at various skeletal sites: a meta-analysis. J.Geriatr.Phys.Ther. 28:102-107.

Pang, M. Y., and Lau, R. W. 2010. The effects of treadmill exercise training on hip bone density and tibial bone geometry in stroke survivors: a pilot study. Neurorehabil.Neural Repair. 24:368-376.

Pang, M. Y., Ashe, M. C., Eng, J. J., McKay, H. A., and Dawson, A. S. 2006. A 19-week exercise program for people with chronic stroke enhances bone geometry at the tibia: a peripheral quantitative computed tomography study. Osteoporos.Int. 17:1615-1625.

Parfitt, A. M. 2002a. Targeted and nontargeted bone remodeling: relationship to basic multicellular unit origination and progression. Bone. 30:5-7.

Parfitt, A. M. 2002b. Misconceptions (2): turnover is always higher in cancellous than in cortical bone. Bone. 30:807-809.

Parfitt, A. M. 2001. The bone remodeling compartment: a circulatory function for bone lining cells. J.Bone Miner.Res. 16:1583-1585.

Parfitt, A. M. 1983. Bone histomorphometry: techniques and interpretation, Ed. Recker, R R, (CRC Press, Boca Raton, 1983), p. 143.

Paschalis, E. P., Shane, E., Lyritis, G., Skarantavos, G., Mendelsohn, R., and Boskey, A. L. 2004. Bone fragility and collagen cross-links. J.Bone Miner.Res. 19:2000-2004.

Pathak, S., Swadener, J. G., Kalidindi, S. R., Courtland, H. W., Jepsen, K. J., and Goldman, H. M. 2011. Measuring the dynamic mechanical response of hydrated mouse bone by nanoindentation. J.Mech.Behav.Biomed.Mater. 4:34-43.

Patsch, J. M., Kiefer, F. W., Varga, P., Pail, P., Rauner, M., Stupphann, D., Resch, H., Moser, D., Zysset, P. K., Stulnig, T. M., and Pietschmann, P. 2011. Increased bone resorption and impaired bone microarchitecture in short-term and extended high-fat diet-induced obesity. Metabolism. 60:243-249.

Paulus, M. J., Gleason, S. S., Easterly, M. E., and Foltz, C. J. 2001. A review of high-resolution X-ray computed tomography and other imaging modalities for small animal research. Lab.Anim.(NY). 30:36-45.

Peacock, M., Turner, C. H., Econs, M. J., and Foroud, T. 2002. Genetics of osteoporosis. Endocr.Rev. 23:303-326.

Perrini, S., Laviola, L., Carreira, M. C., Cignarelli, A., Natalicchio, A., and Giorgino, F. 2010. The GH/IGF1 axis and signaling pathways in the muscle and bone: mechanisms underlying age-related skeletal muscle wasting and osteoporosis. J.Endocrinol. 205:201-210.

Petit, M. A., Beck, T. J., Shults, J., Zemel, B. S., Foster, B. J., and Leonard, M. B. 2005. Proximal femur bone geometry is appropriately adapted to lean mass in overweight children and adolescents. Bone. 36:568-576.

Pettit, A. R., Chang, M. K., Hume, D. A., and Raggatt, L. J. 2008. Osteal macrophages: a new twist on coupling during bone dynamics. Bone. 43:976-982.

Pikkarainen, E., Lehtonen-Veromaa, M., Kautiainen, H., Heinonen, O. J., Viikari, J., and Mottonen, T. 2009. Exercise-induced training effects on bone mineral content: a 7-year follow-up study with adolescent female gymnasts and runners. Scand.J.Med.Sci.Sports. 19:166-173.

Plochocki, J. H., Rivera, J. P., Zhang, C., and Ebba, S. A. 2008. Bone modeling response to voluntary exercise in the hindlimb of mice. J.Morphol. 269:313-318.

Pritchard, J. E., Nowson, C. A., and Wark, J. D. 1996. Bone loss accompanying diet-induced or exercise-induced weight loss: a randomized controlled study. Int.J.Obes.Relat.Metab.Disord. 20:513-520.

Qin, L., Au, S., Choy, W., Leung, P., Neff, M., Lee, K., Lau, M., Woo, J., and Chan, K. 2002. Regular Tai Chi Chuan exercise may retard bone loss in postmenopausal women: A case-control study. Arch.Phys.Med.Rehabil. 83:1355-1359.

Raggatt, L. J., and Partridge, N. C. 2010. Cellular and molecular mechanisms of bone remodeling. J.Biol.Chem. 285:25103-25108.

Ralston, S. H., and Uitterlinden, A. G. 2010. Genetics of osteoporosis. Endocr.Rev. 31:629-662.

Rantalainen, T., Linnamo, V., Komi, P. V., Selanne, H., and 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. Eur.J.Appl.Physiol. 109:651-658.

Rauch, F., Travers, R., and Glorieux, F. H. 2007. Intracortical remodeling during human bone development--a histomorphometric study. Bone. 40:274-280.

Rauch, F., Neu, C., Manz, F., and Schoenau, E. 2001. The development of metaphyseal cortex--implications for distal radius fractures during growth. J.Bone Miner.Res. 16:1547-1555.

Rauch, F., and Schoenau, E. 2001. The developing bone: slave or master of its cells and molecules? Pediatr.Res. 50:309-314.

Raum, K., Leguerney, I., Chandelier, F., Talmant, M., Saied, A., Peyrin, F., and Laugier, P. 2006. Site-matched assessment of structural and tissue properties of cortical bone using scanning acoustic microscopy and synchrotron radiation muCT. Phys.Med.Biol. 51:733-746.

Recker, R. R., Bare, S. P., Smith, S. Y., Varela, A., Miller, M. A., Morris, S. A., and Fox, J. 2009. Cancellous and cortical bone architecture and turnover at the iliac crest of postmenopausal osteoporotic women treated with parathyroid hormone 1-84. Bone. 44:113-119.

Reid, I. R. 2008. Relationships between fat and bone. Osteoporos.Int. 19:595-606.

Reilly, G. C., Knapp, H. F., Stemmer, A., Niederer, P., and Knothe Tate, M. L. 2001. Investigation of the morphology of the lacunocanalicular system of cortical bone using atomic force microscopy. Ann.Biomed.Eng. 29:1074-1081.

Rejnmark, L. 2008. Bone effects of glitazones and other anti-diabetic drugs. Curr.Drug Saf. 3:194-198.

Rho, J. Y., Kuhn-Spearing, L., and Zioupos, P. 1998. Mechanical properties and the hierarchical structure of bone. Med.Eng.Phys. 20:92-102.

Rho, J. Y., Ashman, R. B., and Turner, C. H. 1993. Young's modulus of trabecular and cortical bone material: ultrasonic and microtensile measurements. J.Biomech. 26:111-119.

Rico, H., Revilla, M., Hernandez, E. R., Villa, L. F., and Alvarez del Buergo, M. 1992. Sex differences in the acquisition of total bone mineral mass peak

assessed through dual-energy X-ray absorptiometry. Calcif.Tissue Int. 51:251-254.

Rico, H., Revilla, M., Hernandez, E. R., Villa, L. F., and Lopez-Alonso, A. 1991. Total and regional bone mineral content in normal premenopausal women. Clin.Rheumatol. 10:423-425.

Ritchie, R. O., Koester, K. J., Ionova, S., Yao, W., Lane, N. E., and Ager, J. W.,3rd. 2008. Measurement of the toughness of bone: a tutorial with special reference to small animal studies. Bone. 43:798-812.

Ritman, E. L. 2004. Micro-computed tomography-current status and developments. Annu.Rev.Biomed.Eng. 6:185-208.

Robins, S. P. 2003. Collagen turnover in bone diseases. Curr.Opin.Clin.Nutr.Metab.Care. 6:65-71.

Rogol, A. D. 2010. Sex steroids, growth hormone, leptin and the pubertal growth spurt. Endocr Dev. 17:77-85.

Rogucka, E., Jankowska, E. A., Welon, Z., Medras, M., and Bielicki, T. 2001. Bone mineral status of Polish men in the course of normal ageing. Andrologia. 33:287-292.

Rosen, C. J. 2008. Bone remodeling, energy metabolism, and the molecular clock. Cell.Metab. 7:7-10.

Rosen, C. J., and Bouxsein, M. L. 2006. Mechanisms of disease: is osteoporosis the obesity of bone? Nat.Clin.Pract.Rheumatol. 2:35-43.

Roux, C. 2001. Can practitioners use the WHO definition for osteoporosis? Joint Bone Spine. 68:10-11.

Rubin, M. A., Rubin, J., and Jasiuk, I. 2004. SEM and TEM study of the hierarchical structure of C57BL/6J and C3H/HeJ mice trabecular bone. Bone. 35:11-20.

Ruff, C. B., and Hayes, W. C. 1982. Subperiosteal expansion and cortical remodeling of the human femur and tibia with aging. Science. 217:945-948.

Ruppel, M. E., Miller, L. M., and Burr, D. B. 2008. The effect of the microscopic and nanoscale structure on bone fragility. Osteoporos.Int. 19:1251-1265.

Russell, M., Mendes, N., Miller, K. K., Rosen, C. J., Lee, H., Klibanski, A., and Misra, M. 2010. Visceral fat is a negative predictor of bone density measures in obese adolescent girls. J.Clin.Endocrinol.Metab. 95:1247-1255.

Sabsovich, I., Clark, J. D., Liao, G., Peltz, G., Lindsey, D. P., Jacobs, C. R., Yao, W., Guo, T. Z., and Kingery, W. S. 2008. Bone microstructure and its associated genetic variability in 12 inbred mouse strains: microCT study and in silico genome scan. Bone. 42:439-451.

Saito, M., and Marumo, K. 2010. Collagen cross-links as a determinant of bone quality: a possible explanation for bone fragility in aging, osteoporosis, and diabetes mellitus. Osteoporos.Int. 21:195-214.

Sakata, S., Barkmann, R., Lochmuller, E. M., Heller, M., and Gluer, C. C. 2004. Assessing bone status beyond BMD: evaluation of bone geometry and porosity by quantitative ultrasound of human finger phalanges. J.Bone Miner.Res. 19:924-930.

Sanchez, M. M., and Gilsanz, V. 2005. Pediatric DXA bone measurements. Pediatr.Endocrinol.Rev. 2 Suppl 3:S337-341.

Sardinha, L. B., Baptista, F., and Ekelund, U. 2008. Objectively measured physical activity and bone strength in 9-year-old boys and girls. Pediatrics. 122:e728-736.

Saura, M., Tarin, C., and Zaragoza, C. 2010. Recent insights into the implication of nitric oxide in osteoblast differentiation and proliferation during bone development. ScientificWorldJournal. 10:624-632.

Schaffler, M. B. 2003. Role of bone turnover in microdamage. Osteoporos.Int. 14 Suppl 5:S73-7; discussion S77-80.

Schaffler, M. B., Choi, K., and Milgrom, C. 1995. Aging and matrix microdamage accumulation in human compact bone. Bone. 17:521-525.

Schneider, M., Dunton, G. F., Bassin, S., Graham, D. J., Eliakim, A. F., and Cooper, D. M. 2007a. Impact of a school-based physical activity intervention on fitness and bone in adolescent females. J.Phys.Act.Health. 4:17-29.

Schneider, P., Stauber, M., Voide, R., Stampanoni, M., Donahue, L. R., and Muller, R. 2007b. Ultrastructural properties in cortical bone vary greatly in two inbred strains of mice as assessed by synchrotron light based micro- and nano-CT. J.Bone Miner.Res. 22:1557-1570.

Schulzke, S. M., Trachsel, D., and Patole, S. K. 2007. Physical activity programs for promoting bone mineralization and growth in preterm infants. Cochrane Database Syst.Rev. (2):CD005387.

Seeman, E., and Delmas, P. D. 2006. Bone quality--the material and structural basis of bone strength and fragility. N.Engl.J.Med. 354:2250-2261.

Seeman, E. 2003. Periosteal bone formation--a neglected determinant of bone strength. N.Engl.J.Med. 349:320-323.

Segal, N. A., Torner, J. C., Yang, M., Curtis, J. R., Felson, D. T., Nevitt, M. C., and Multicenter Osteoarthritis Study Group. 2008. Muscle mass is more strongly related to hip bone mineral density than is quadriceps strength or lower activity level in adults over age 50 year. J.Clin.Densitom. 11:503-510.

Seibel, M. J. 2005. Biochemical markers of bone turnover: part I: biochemistry and variability. Clin.Biochem.Rev. 26:97-122.

Seibel, M. J. 2002. Nutrition and molecular markers of bone remodelling. Curr.Opin.Clin.Nutr.Metab.Care. 5:525-531.

Shaffer, J. R., Kammerer, C. M., Bruder, J. M., Cole, S. A., Dyer, T. D., Almasy, L., MacCluer, J. W., Blangero, J., Bauer, R. L., and Mitchell, B. D. 2008. Genetic influences on bone loss in the San Antonio Family Osteoporosis Study. Osteoporos.Int. 19:1759-1767.

Shankar, K., Hidestrand, M., Liu, X., Chen, J. R., Haley, R., Perrien, D. S., Skinner, R. A., Lumpkin, C. K.,Jr, Badger, T. M., and Ronis, M. J. 2008. Chronic ethanol consumption inhibits postlactational anabolic bone rebuilding in female rats. J.Bone Miner.Res. 23:338-349.

Shaw, C. N., and Stock, J. T. 2009. Intensity, repetitiveness, and directionality of habitual adolescent mobility patterns influence the tibial diaphysis morphology of athletes. Am.J.Phys.Anthropol. 140:149-159.

Sievänen, H. 2000. A physical model of dual-energy X-ray absorptiometry—derived bone mineral density. Invest.Radio. 35:325-330.

Sievänen, H., and Kannus, P. 2007. Physical activity reduces the risk of fragility fracture. PLoS Med. 4:e222.

Silva, M. J., and Gibson, L. J. 1997. Modeling the mechanical behavior of vertebral trabecular bone: effects of age-related changes in microstructure. Bone. 21:191-199.

Sims, N. A., and Gooi, J. H. 2008. Bone remodeling: Multiple cellular interactions required for coupling of bone formation and resorption. Semin.Cell Dev.Biol. 19:444-451.

Sievänen, H., Kannus, P., and Järvinen, T. L. 2007. Bone quality: an empty term. PloS Med. 4: e27.

Sievänen, H. 2008. Measuring small changes versus measurement error. J.Bone Miner.Res. 23:576-577.

Singh, S. P., Chang, E. I., Gossain, A. K., Mehara, B. J., Galiano, R. D., Jensen, J., Longaker, M. T., Gurtner, G. C., and Saadeh, P. B. 2007. Cyclic mechanical strain increases production of regulators of bone healing in cultured murine osteoblasts. J.Am.Coll.Surg. 204:426-434.

Slemenda, C. W., Longcope, C., Zhou, L., Hui, S. L., Peacock, M., and Johnston, C. C. 1997. Sex steroids and bone mass in older men. Positive associations with serum estrogens and negative associations with androgens. J.Clin.Invest. 100:1755-1759.

Smith, R. W., and Walker, R. R. 1964. Femoral expansion in aging women: implications for osteoporosis and fractures. Science. 145:156-157.

Smock, A. J., Hughes, J. M., Popp, K. L., Wetzsteon, R. J., Stovitz, S. D., Kaufman, B. C., Kurzer, M. S., and Petit, M. A. 2009. Bone volumetric density, geometry, and strength in female and male collegiate runners. Med.Sci.Sports Exerc. 41:2026-2032.

Sodek, J., Zhu, B., Huynh, M. H., Brown, T. J., and Ringuette, M. 2002. Novel functions of the matricellular proteins osteopontin and osteonectin/SPARC. Connect.Tissue Res. 43:308-319.

Somerville, J. M., Aspden, R. M., Armour, K. E., Armour, K. J., and Reid, D. M. 2004. Growth of C57BL/6 mice and the material and mechanical properties of cortical bone from the tibia. Calcif.Tissue Int. 74:469-475.

Sone, T., Imai, Y., Joo, Y. I., Onodera, S., Tomomitsu, T., and Fukunaga, M. 2006. Side-to-side differences in cortical bone mineral density of tibiae in young male athletes. Bone. 38:708-713.

Song, G., Ju, Y., Shen, X., Luo, Q., Shi, Y., and Qin, J. 2007. Mechanical stretch promotes proliferation of rat bone marrow mesenchymal stem cells. Colloids Surf.B Biointerfaces. 58:271-277.

Sorock, G. S., Bush, T. L., Golden, A. L., Fried, L. P., Breuer, B., and Hale, W. E. 1988. Physical activity and fracture risk in a free-living elderly cohort. J.Gerontol. 43:M134-9.

Specker, B., and Binkley, T. 2003. Randomized trial of physical activity and calcium supplementation on bone mineral content in 3- to 5-year-old children. J.Bone Miner.Res. 18:885-892.

Stein, M. S., Feik, S. A., Thomas, C. D., Clement, J. G., and Wark, J. D. 1999. An automated analysis of intracortical porosity in human femoral bone across age. J.Bone Miner.Res. 14:624-632.

Stepensky, D., Kleinberg, L., and Hoffman, A. 2003. Bone as an effect compartment : models for uptake and release of drugs. Clin.Pharmacokinet. 42:863-881.

Stettler, N., Berkowtiz, R. I., Cronquist, J. L., Shults, J., Wadden, T. A., Zemel, B. S., and Leonard, M. B. 2008. Observational study of bone accretion during successful weight loss in obese adolescents. Obesity (Silver Spring). 16:96-101.

Stewart, K. J., Bacher, A. C., Hees, P. S., Tayback, M., Ouyang, P., and Jan de, B. S. Am.J.Prev.Med. 28:453-460.

Stransky, M., and Rysava, L. 2009. Nutrition as prevention and treatment of osteoporosis. Physiol.Res. 58 Suppl 1:S7-S11.

Streeten, E. A., Beck, T. J., O'Connell, J. R., Rampersand, E., McBride, D. J., Takala, S. L., Pollin, T. I., Uusi-Rasi, K., Mitchell, B. D., and Shuldiner, A. R. 2008. Autosome-wide linkage analysis of hip structural phenotypes in the Old Order Amish. Bone. 43:607-612.

Su, X., Sun, K., Cui, F. Z., and Landis, W. J. 2003. Organization of apatite crystals in human woven bone. Bone. 32:150-162.

Sukumar, D., Schlussel, Y., Riedt, C. S., Gordon, C., Stahl, T., and Shapses, S. A. 2010. Obesity alters cortical and trabecular bone density and geometry in women. Osteoporos.Int. 22:635-645.

Suominen, H. 2006. Muscle training for bone strength. Aging Clin.Exp.Res. 18:85-93.

Suvorova, E. I., Petrenko, P. P., and Buffat, P. A. 2007. Scanning and transmission electron microscopy for evaluation of order/disorder in bone structure. Scanning. 29:162-170.

Szulc, P., and Delmas, P. D. 2007. Bone loss in elderly men: increased endosteal bone loss and stable periosteal apposition. The prospective MINOS study. Osteoporos.Int. 18:495-503.

Szulc, P., Seeman, E., Duboeuf, F., Sornay-Rendu, E., and Delmas, P. D. 2006. Bone fragility: failure of periosteal apposition to compensate for increased endocortical resorption in postmenopausal women. J.Bone Miner.Res. 21:1856-1863.

Tachi, K., Takami, M., Zhao, B., Mochizuki, A., Yamada, A., Miyamoto, Y., Inoue, T., Baba, K., and Kamijo, R. 2010. Bone morphogenetic protein 2 enhances mouse osteoclast differentiation via increased levels of receptor

activator of NF-kappaB ligand expression in osteoblasts. Cell Tissue Res. 342:213-220.

Taes, Y., Lapauw, B., Vanbillemont, G., Bogaert, V., De Bacquer, D., Goemaere, S., Zmierczak, H., and Kaufman, J. M. 2010. Early smoking is associated with peak bone mass and prevalent fractures in young, healthy men. J.Bone Miner.Res. 25:379-387.

Tai, K., Qi, H. J., and Ortiz, C. 2005. Effect of mineral content on the nanoindentation properties and nanoscale deformation mechanisms of bovine tibial cortical bone. J.Mater.Sci.Mater.Med. 16:947-959.

Tam, W. Y., Chook, P., Qiao, M., Chan, L. T., Chan, T. Y., Poon, Y. K., Fung, K. P., Leung, P. C., and Woo, K. S. 2009. The efficacy and tolerability of adjunctive alternative herbal medicine (Salvia miltiorrhiza and Pueraria lobata) on vascular function and structure in coronary patients. J.Altern.Complement.Med. 15:415-421.

Tamaki, J., Iki, M., Fujita, Y., Kouda, K., Yura, A., Kadowaki, E., Sato, Y., Moon, J. S., Tomioka, K., Okamoto, N., and Kurumatani, N. 2010. Impact of smoking on bone mineral density and bone metabolism in elderly men: the Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) study. Osteoporos.Int. 22:133-141.

Tamaki, J., Ikeda, Y., Morita, A., Sato, Y., Naka, H., and Iki, M. 2008. Which element of physical activity is more important for determining bone growth in Japanese children and adolescents: the degree of impact, the period, the frequency, or the daily duration of physical activity? J.Bone Miner.Metab. 26:366-372.

Tatsumi, S., Ishii, K., Amizuka, N., Li, M., Kobayashi, T., Kohno, K., Ito, M., Takeshita, S., and Ikeda, K. 2007. Targeted ablation of osteocytes induces osteoporosis with defective mechanotransduction. Cell.Metab. 5:464-475.

Techawiboonwong, A., Song, H. K., Leonard, M. B., and Wehrli, F. W. 2008. Cortical bone water: *in vivo* quantification with ultrashort echo-time MR imaging. Radiology. 248:824-833.

Teegarden, D., Proulx, W. R., Martin, B. R., Zhao, J., McCabe, G. P., Lyle, R. M., Peacock, M., Slemenda, C., Johnston, C. C., and Weaver, C. M. 1995. Peak bone mass in young women. J.Bone Miner.Res. 10:711-715.

Terrier, A., Miyagaki, J., Fujie, H., Hayashi, K., and Rakotomanana, L. 2005. Delay of intracortical bone remodelling following a stress change: a theoretical and experimental study. Clin.Biomech.(Bristol, Avon). 20:998-1006.

Tervo, T., Nordstrom, P., Neovius, M., and Nordstrom, A. 2009. Reduced physical activity corresponds with greater bone loss at the trabecular than the cortical bone sites in men. Bone. 45:1073-1078.

Thommesen, L., Stunes, A. K., Monjo, M., Grosvik, K., Tamburstuen, M. V., Kjobli, E., Lyngstadaas, S. P., Reseland, J. E., and Syversen, U. 2006. Expression and regulation of resistin in osteoblasts and osteoclasts indicate a role in bone metabolism. J.Cell.Biochem. 99:824-834.

Thomsen, J. S., Ebbesen, E. N., and Mosekilde, L. 2002. Predicting human vertebral bone strength by vertebral static histomorphometry. Bone. 30:502-508.

Thorpe, D. L., Knutsen, S. F., Beeson, W. L., and Fraser, G. E. 2006. The effect of vigorous physical activity and risk of wrist fracture over 25 years in a low-risk survivor cohort. J.Bone Miner.Metab. 24:476-483.

Thurner, P. J., Chen, C. G., Ionova-Martin, S., Sun, L., Harman, A., Porter, A., Ager, J. W.,3rd, Ritchie, R. O., and Alliston, T. 2010. Osteopontin deficiency increases bone fragility but preserves bone mass. Bone. 46:1564-1573.

Thurner, P. J. 2009. Atomic force microscopy and indentation force measurement of bone. Wiley Interdiscip.Rev.Nanomed Nanobiotechnol. 1:624-649.

Tong, W., Glimcher, M. J., Katz, J. L., Kuhn, L., and Eppell, S. J. 2003. Size and shape of mineralites in young bovine bone measured by atomic force microscopy. Calcif.Tissue Int. 72:592-598.

Totosy de Zepetnek, J. O., Giangregorio, L. M., and Craven, B. C. 2009. Whole-body vibration as potential intervention for people with low bone mineral density and osteoporosis: a review. J.Rehabil.Res.Dev. 46:529-542.

Tourinho, T. F., Capp, E., Brenol, J. C., and Stein, A. 2008. Physical activity prevents bone loss in premenopausal women with rheumatoid arthritis: a cohort study. Rheumatol.Int. 28:1001-1007.

Tran Van, P., Vignery, A., and Baron, R. 1982a. An electron-microscopic study of the bone-remodeling sequence in the rat. Cell Tissue Res. 225:283-292.

Tran Van, P. T., Vignery, A., and Baron, R. 1982b. Cellular kinetics of the bone remodeling sequence in the rat. Anat.Rec. 202:445-451.

Trutschnigg, B., Chong, C., Habermayerova, L., Karelis, A. D., and Komorowski, J. 2008. Female boxers have high bone mineral density despite low body fat mass, high energy expenditure, and a high incidence of oligomenorrhea. Appl.Physiol.Nutr.Metab. 33:863-869.

Tse, K. Y., Macias, B. R., Meyer, R. S., and Hargens, A. R. 2009. Heritability of bone density: regional and gender differences in monozygotic twins. J.Orthop.Res. 27:150-154.

Turner, C. H. 2006. Bone strength: current concepts. Ann.N.Y.Acad.Sci. 1068:429-446.

Turner, C. H. 2002. Biomechanics of bone: determinants of skeletal fragility and bone quality. Osteoporos.Int. 13:97-104.

Turner, C. H. 1998. Three rules for bone adaptation to mechanical stimuli. Bone. 23:399-407.

Turner, C. H., and Pavalko, F. M. 1998. Mechanotransduction and functional response of the skeleton to physical stress: the mechanisms and mechanics of bone adaptation. J.Orthop.Sci. 3:346-355.

Tylavsky, F. A., Ryder, K. A., Lyytikainen, A., and Cheng, S. 2005. Vitamin D, parathyroid hormone, and bone mass in adolescents. J.Nutr. 135:2735S-8S.

Ulrich, D., van Rietbergen, B., Laib, A., and Ruegsegger, P. 1999. The ability of three-dimensional structural indices to reflect mechanical aspects of trabecular bone. Bone. 25:55-60.

Umemura, Y., Baylink, D. J., Wergedal, J. E., Mohan, S., and Srivastava, A. K. 2002. A time course of bone response to jump exercise in C57BL/6J mice. J.Bone Miner.Metab. 20:209-215.

Unnanuntana, A., Rebolledo, B. J., Michael Khair, M., Dicarlo, E. F., and Lane, J. M. 2010. Diseases affecting bone quality: beyond osteoporosis. Clin.Orthop.Relat.Res. 469:2194-2206.

Ural, A., and Vashishth, D. 2007. Effects of intracortical porosity on fracture toughness in aging human bone: a microCT-based cohesive finite element study. J.Biomech.Eng. 129:625-631.

Utku, F. S., Klein, E., Saybasili, H., Yucesoy, C. A., and Weiner, S. 2008. Probing the role of water in lamellar bone by dehydration in the environmental scanning electron microscope. J.Struct.Biol. 162:361-367.

Utting, J. C., Flanagan, A. M., Brandao-Burch, A., Orriss, I. R., and Arnett, T. R. 2010. Hypoxia stimulates osteoclast formation from human peripheral blood. Cell Biochem.Funct. 28:374-380.

Utting, J. C., Robins, S. P., Brandao-Burch, A., Orriss, I. R., Behar, J., and Arnett, T. R. 2006. Hypoxia inhibits the growth, differentiation and bone-forming capacity of rat osteoblasts. Exp.Cell Res. 312:1693-1702.

Uusi-Rasi, K., Kannus, P., Pasanen, M., and Sievänen, H. 2010a. Is childhood obesity associated with bone density and strength in adulthood? J.Osteoporos. 2010:904806.

Uusi-Rasi, K., Rauhio, A., Kannus, P., Pasanen, M., Kukkonen-Harjula, K., Fogelholm, M., and Sievänen, H. 2010b. Three-month weight reduction does not compromise bone strength in obese premenopausal women. Bone. 46:1286-1293.

Uusi-Rasi, K., Sievänen, H., Heinonen, A., Vuori, I., Beck, T. J., and Kannus, P. 2006. Long-term recreational gymnastics provides a clear benefit in age-related functional decline and bone loss. A prospective 6-year study. Osteoporos.Int. 17:1154-1164.

Uusi-Rasi, K., Kannus, P., Cheng, S., Sievänen, H., Pasanen, M., Heinonen, A., Nenonen, A., Halleen, J., Fuerst, T., Genant, H., and Vuori, I. 2003. Effect of alendronate and exercise on bone and physical performance of postmenopausal women: a randomized controlled trial. Bone. 33:132-143.

Uusi-Rasi, K., Sievänen, H., Pasanen, M., Oja, P., and Vuori, I. 2002. Associations of calcium intake and physical activity with bone density and size in premenopausal and postmenopausal women: a peripheral quantitative computed tomography study. J.Bone Miner.Res. 17:544-552.

Uzunca, K., Birtane, M., Durmus-Altun, G., and Ustun, F. 2005. High bone mineral density in loaded skeletal regions of former professional football (soccer) players: what is the effect of time after active career? Br.J.Sports Med. 39:154-7; discussion 154-7.

Väänänen, H. K., and Laitala-Leinonen, T. 2008. Osteoclast lineage and function. Arch.Biochem.Biophys. 473:132-138.

Vainionpää, A., Korpelainen, R., Sievänen, H., Vihriälä, E., Leppäluoto, J., and Jämsä, T. 2007. Effect of impact exercise and its intensity on bone geometry at weight-bearing tibia and femur. Bone. 40:604-611.

Vainionpää, A., Korpelainen, R., Vihriälä, E., Rinta-Paavola, A., Leppäluoto, J., and Jämsä, T. 2006. Intensity of exercise is associated with bone density change in premenopausal women. Osteoporos.Int. 17:455-463.

Vajda, E. G., Wronski, T. J., Halloran, B. P., Bachus, K. N., and Miller, S. C. 2001. Spaceflight alters bone mechanics and modeling drifts in growing rats. Aviat.Space Environ.Med. 72:720-726.

Valdimarsson, O., Alborg, H. G., Duppe, H., Nyquist, F., and Karlsson, M. 2005. Reduced training is associated with increased loss of BMD. J.Bone Miner.Res. 20:906-912.

Valverde, P., Zhang, J., Fix, A., Zhu, J., Ma, W., Tu, Q., and Chen, J. 2008. Overexpression of bone sialoprotein leads to an uncoupling of bone formation and bone resorption in mice. J.Bone Miner.Res. 23:1775-1788.

Vatanparast, H., Baxter-Jones, A., Faulkner, R. A., Bailey, D. A., and Whiting, S. J. 2005. Positive effects of vegetable and fruit consumption and calcium intake on bone mineral accrual in boys during growth from childhood to adolescence: the University of Saskatchewan Pediatric Bone Mineral Accrual Study. Am.J.Clin.Nutr. 82:700-706.

Vehmas, T., Solovieva, S., Riihimaki, H., Luoma, K., and Leino-Arjas, P. 2005. Hand workload and the metacarpal cortical index. a study of middle-aged teachers and dentists. Osteoporos.Int. 16:672-680.

Vicente-Rodriguez, G., Dorado, C., Perez-Gomez, J., Gonzalez-Henriquez, J. J., and Calbet, J. A. 2004. Enhanced bone mass and physical fitness in young female handball players. Bone. 35:1208-1215.

Villareal, D. T., Fontana, L., Wess, E. P., Racette, S. B., Steger-May, K., Schechtman, K. B., Klein, S., and Holloszy, J. O. Arch.Intern.Med. 166:2502-2510.

Vujasinovic-Stupar, N., Milic, N., Petrovic-Rackov, L., Prodanovic, N., Mijailovic-Ivkovic, M., Grujic, Z., Bukovic, S., Novkovic, S., Pasalic-Simic, K., Petrovic, V., Vukasinovic, D., Perunicic, G., and ESTHER Study Group. 2010. Efficacy and safety of once monthly ibandronate treatment in patients with reduced bone mineral density--ESTHER study. Srp.Arh.Celok.Lek. 138:56-61.

Waarsing, J. H., Day, J. S., and Weinans, H. 2004. An improved segmentation method for *in vivo* microCT imaging. J.Bone Miner.Res. 19:1640-1650.

Wachter, N. J., Krischak, G. D., Mentzel, M., Sarkar, M. R., Ebinger, T., Kinzl, L., Claes, L., and Augat, P. 2002. Correlation of bone mineral density with strength and microstructural parameters of cortical bone *in vitro*. Bone. 31:90-95.

Wallace, J. M., Erickson, B., Les, C. M., Orr, B. G., and Banaszak Holl, M. M. 2010. Distribution of type I collagen morphologies in bone: relation to estrogen depletion. Bone. 46:1349-1354.

Wallace, J. M., Rajachar, R. M., Allen, M. R., Bloomfield, S. A., Robey, P. G., Young, M. F., and Kohn, D. H. 2007. Exercise-induced changes in the cortical bone of growing mice are bone- and gender-specific. Bone. 40:1120-1127.

Wang, X., Kammerer, C. M., Wheeler, V. W., Patrick, A. L., Bunker, C. H., and Zmuda, J. M. 2007a. Genetic and environmental determinants of volumetric and areal BMD in multi-generational families of African ancestry: the Tobago Family Health Study. J.Bone Miner.Res. 22:527-536.

Wang, X., Masse, D. B., Leng, H., Hess, K. P., Ross, R. D., Roeder, R. K., and Niebur, G. L. 2007b. Detection of trabecular bone microdamage by micro-computed tomography. J.Biomech. 40:3397-3403.

Wang, X., and Niebur, G. L. 2006. Microdamage propagation in trabecular bone due to changes in loading mode. J.Biomech. 39:781-790.

Wang, X., and Puram, S. 2004. The toughness of cortical bone and its relationship with age. Ann.Biomed.Eng. 32:123-135.

Wang, X., Bank, R. A., TeKoppele, J. M., and Agrawal, C. M. 2001. The role of collagen in determining bone mechanical properties. J.Orthop.Res. 19:1021-1026.

Ward, K., Alsop, C., Caulton, J., Rubin, C., Adams, J., and Mughal, Z. 2004. Low magnitude mechanical loading is osteogenic in children with disabling conditions. J.Bone Miner.Res. 19:360-369.

Ward, K. A., Roberts, S. A., Adams, J. E., Lanham-New, S., and Mughal, M. Z. 2007. Calcium supplementation and weight bearing physical activity--do they have a combined effect on the bone density of pre-pubertal children? Bone. 41:496-504.

Warner, S. E., Shea, J. E., Miller, S. C., and Shaw, J. M. 2006. Adaptations in cortical and trabecular bone in response to mechanical loading with and without weight bearing. Calcif.Tissue Int. 79:395-403.

Warren, G. L., Moran, A. L., Hogan, H. A., Lin, A. S., Guldberg, R. E., and Lowe, D. A. 2007. Voluntary run training but not estradiol deficiency alters the tibial bone-soleus muscle functional relationship in mice. Am.J.Physiol.Regul.Integr.Comp.Physiol. 293:R2015-2026.

Watkins, B. A., Li, Y., Allen, K. G., Hoffmann, W. E., and Seifert, M. F. 2000. Dietary ratio of (n-6)/(n-3) polyunsaturated fatty acids alters the fatty acid composition of bone compartments and biomarkers of bone formation in rats. J.Nutr. 130:2274-2284.

Weaver, C. M. 2008. The role of nutrition on optimizing peak bone mass. Asia Pac.J.Clin.Nutr. 17 Suppl 1:S135-137.

Weeks, B. K., Young, C. M., and Beck, B. R. 2008. Eight months of regular in-school jumping improves indices of bone strength in adolescent boys and Girls: the POWER PE study. J.Bone Miner.Res. 23:1002-1011.

Weiler, U., Salloum, B. A., and Claus, R. 2006. Influence of short-term confinement and exercise on tibia development in growing pigs. J.Vet.Med.A Physiol.Pathol.Clin.Med. 53:450-455.

Weisberg, S. P., McCann, D., Desai, M., Rosenbaum, M., Leibel, R. L., and Ferrante, A. W.,Jr. 2003. Obesity is associated with macrophage accumulation in adipose tissue. J.Clin.Invest. 112:1796-1808.

Welch, J. M., Turner, C. H., Devareddy, L., Arjmandi, B. H., and Weaver, C. M. 2008. High impact exercise is more beneficial than dietary calcium for building bone strength in the growing rat skeleton. Bone. 42:660-668.

Wetzsteon, R. J., Petit, M. A., Macdonald, H. M., Hughes, J. M., Beck, T. J., and McKay, H. A. 2008. Bone structure and volumetric BMD in overweight children: a longitudinal study. J.Bone Miner.Res. 23:1946-1953.

Wilson, E. E., Awonusi, A., Morris, M. D., Kohn, D. H., Tecklenburg, M. M., and Beck, L. W. 2006. Three structural roles for water in bone observed by solid-state NMR. Biophys.J. 90:3722-3731.

Wilson, E. E., Awonusi, A., Morris, M. D., Kohn, D. H., Tecklenburg, M. M., and Beck, L. W. 2005. Highly ordered interstitial water observed in bone by nuclear magnetic resonance. J.Bone Miner.Res. 20:625-634.

Winkler, I. G., Sims, N. A., Pettit, A. R., Barbier, V., Nowlan, B., Helwani, F., Poulton, I. J., van Rooijen, N., Alexander, K. A., Raggatt, L. J., and Levesque, J. P. 2010. Bone marrow macrophages maintain hematopoietic stem cell (HSC) niches and their depletion mobilizes HSCs. Blood. 116:4815-4828.

Winzenberg, T., Shaw, K., Fryer, J., and Jones, G. 2006. Effects of calcium supplementation on bone density in healthy children: meta-analysis of randomised controlled trials. BMJ. 333:775.

Wren, T. A., and Gilsanz, V. 2006. Assessing bone mass in children and adolescents. Curr.Osteoporos Rep. 4:153-158.

Wu, J., Wang, X. X., Higuchi, M., Yamada, K., and Ishimi, Y. 2004. High bone mass gained by exercise in growing male mice is increased by subsequent reduced exercise. J.Appl.Physiol. 97:806-810.

Wu, J. Y., Scadden, D. T., and Kronenberg, H. M. 2009. Role of the osteoblast lineage in the bone marrow hematopoietic niches. J.Bone Miner.Res. 24:759-764.

Wu, Y., Dai, G., Ackerman, J. L., Hrovat, M. I., Glimcher, M. J., Snyder, B. D., Nazarian, A., and Chesler, D. A. 2007. Water- and fat-suppressed proton projection MRI (WASPI) of rat femur bone. Magn.Reson.Med. 57:554-567.

Wust, R. C., Winwood, K., Wilks, D. C., Morse, C. I., Degens, H., and Rittweger, J. 2010. Effects of smoking on tibial and radial bone mass and strength may diminish with age. J.Clin.Endocrinol.Metab. 95:2763-2771.

Xiong, D. H., Liu, Y. Z., Liu, P. Y., Zhao, L. J., and Deng, H. W. 2005. Association analysis of estrogen receptor alpha gene polymorphisms with cross-sectional geometry of the femoral neck in Caucasian nuclear families. Osteoporos.Int. 16:2113-2122.

Xu, J., Rho, J. Y., Mishra, S. R., and Fan, Z. 2003. Atomic force microscopy and nanoindentation characterization of human lamellar bone prepared by microtome sectioning and mechanical polishing technique. J.Biomed.Mater.Res.A. 67:719-726.

Xu, S., and Yu, J. J. 2006. Beneath the minerals, a layer of round lipid particles was identified to mediate collagen calcification in compact bone formation. Biophys.J. 91:4221-4229.

Yamashita, T., Nabeshima, Y., and Noda, M. 2000. High-resolution micro-computed tomography analyses of the abnormal trabecular bone structures in klotho gene mutant mice. J.Endocrinol. 164:239-245.

Yan, J., Daga, A., Kumar, R., and Mecholsky, J. J. 2008. Fracture toughness and work of fracture of hydrated, dehydrated, and ashed bovine bone. J.Biomech. 41:1929-1936.

Yannakoulia, M., Keramopoulos, A., and Matalas, A. L. 2004. Bone mineral density in young active females: the case of dancers. Int.J.Sport Nutr.Exerc.Metab. 14:285-297.

Yavropoulou, M. P., and Yovos, J. G. 2008. Osteoclastogenesis--current knowledge and future perspectives. J.Musculoskelet.Neuronal Interact. 8:204-216.

Yeni, Y. N., Brown, C. U., Wang, Z., and Norman, T. L. 1997. The influence of bone morphology on fracture toughness of the human femur and tibia. Bone. 21:453-459.

Yin, J., Zhang, Q., Liu, A., Du, W., Wang, X., Hu, X., and Ma, G. 2010. Calcium supplementation for 2 years improves bone mineral accretion and lean body mass in Chinese adolescents. Asia Pac.J.Clin.Nutr. 19:152-160.

Young, C. M., Weeks, B. K., and Beck, B. R. 2007. Simple, novel physical activity maintains proximal femur bone mineral density, and improves muscle strength and balance in sedentary, postmenopausal Caucasian women. Osteoporos.Int. 18:1379-1387.

Zalloua, P. A., Hsu, Y. H., Terwedow, H., Zang, T., Wu, D., Tang, G., Li, Z., Hong, X., Azar, S. T., Wang, B., Bouxsein, M. L., Brain, J., Cummings, S. R., Rosen, C. J., and Xu, X. 2007. Impact of seafood and fruit consumption on bone mineral density. Maturitas. 56:1-11.

Zebaze, R. M., Ghasem-Zadeh, A., Bohte, A., Iuliano-Burns, S., Mirams, M., Price, R. I., Mackie, E. J., and Seeman, E. 2010. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. Lancet. 375:1729-1736.

Zhai, G., Andrew, T., Kato, B. S., Blake, G. M., and Spector, T. D. 2009. Genetic and environmental determinants on bone loss in postmenopausal Caucasian women: a 14-year longitudinal twin study. Osteoporos.Int. 20:949-953.

Zhang, P., Su, M., Tanaka, S. M., and Yokota, H. 2006. Knee loading stimulates cortical bone formation in murine femurs. BMC Musculoskelet.Disord. 7:73.

Zhang, Y., Cui, F. Z., Wang, X. M., Feng, Q. L., and Zhu, X. D. 2002. Mechanical properties of skeletal bone in gene-mutated stopsel(dtl28d) and wild-type zebrafish (Danio rerio) measured by atomic force microscopy-based nanoindentation. Bone. 30:541-546.

Zioupos, P., and Currey, J. D. 1998. Changes in the stiffness, strength, and toughness of human cortical bone with age. Bone. 22:57-66.

Zizak, I., Roschger, P., Paris, O., Misof, B. M., Berzlanovich, A., Bernstorff, S., Amenitsch, H., Klaushofer, K., and Fratzl, P. 2003. Characteristics of mineral particles in the human bone/cartilage interface. J.Struct.Biol. 141:208-217.

1 KIRJONEN, JUHANI, On the description of a human movement and its psychophysical correlates under psychomotor loads. 48 p. 1971.
2 KIRJONEN, JUHANI JA RUSKO, HEIKKI, Liikkeen kinemaattisista ominaispiirteistä, niiden psykofyysisistä selitysyhteyksistä ja näiden muutoksista psykomotorisen kuormituksen ja kestävyysharjoittelun vaikutuksesta. - On the kinematic charac-teristics and psychophysical correlates of a human movement and their changes during psychomotor loading and endurace conditioning. 156 p. 1971.
3 SARVIHARJU, PEKKA J., Effects of psycho-physical loading and progressive endurance conditioning on selected biochemical correlates of adaptive responses in man. 95 p. 1973.
4 KIVIAHO, PEKKA, Sport organizations and the structure of society. 54 p. 1973.
5 KOMI, PAAVO V., NELSON, RICHARD C. AND PULLI, MATTI, Biomechanics of skijumping. 53 p. 1974.
6 METELI, Työolot, terveys ja liikuntakäyttäytyminen metallitehtaissa. Kartoittavan kyselyn aineistot ja toteuttaminen. 178 p. 1974.
7 TIAINEN, JORMA M., Increasing physical education students' creative thinking. 53 p. 1976.
8 RUSKO, HEIKKI, Physical performance characteristics in Finnish athletes. 40 p. 1976.
9 KIISKINEN, ANJA, Adaptation of connective tissues to physical training in young mice. 43 p. 1976.
10 VUOLLE, PAULI, Urheilu elämänsisältönä. Menestyneiden urheilijoiden elämänura kilpailuvuosina - Top sport as content of life. 227 p. 1977.
11 SUOMINEN, HARRI, Effects of physical training in middle-aged and elderly people with special regard to skeletal muscle, connective tissue, and functional aging. 40 p. 1978.
12 VIITASALO, JUKKA, Neuromuscular performance in voluntary and reflex contraction with special reference to muscle structure and fatigue. 59 p. 1980.
13 LUHTANEN, PEKKA, On the mechanics of human movement with special reference to walking, running and jumping. 58 p. 1980.
14 LAAKSO, LAURI, Lapsuuden ja nuoruuden kasvuympäristö aikuisiän liikuntaharrastusten selittäjänä: retrospektiivinen tutkimus. - Socialization environment in childhood and youth as determinant of adult-age sport involvement: a retrospective study. 295 p. 1981.
15 BOSCO, CARMELO, Stretch-schortening cycle inskeletal muscle function with special reference to elastic energy and potentiation of myoelectrical activity. 64 p. 1982.
16 OLIN, KALEVI, Päätöksentekijöiden viiteryhmät kaupunkien liikuntapolitiikassa. - Reference groups of decision-makers in the sport politics of cities. 155 p. 1982.
17 KANNAS, LASSE, Tupakointia koskeva terveyskasvatus peruskoulussa. - Health education on smoking in the Finnish comprehensive school. 251 p. 1983.
18 Contribution of sociology to the study of sport. Festschrift Book in Honour of Professor Kalevi Heinilä. Ed. by OLIN, K. 243 p. 1984.
19 ALÉN, MARKKU, Effects of self-administered, high-dose testosterone and anabolic steroids on serum hormones, lipids, enzymes and on spermatogenesis in power athletes. 75 p. 1985.
20 HÄKKINEN, KEIJO, Training and detraining adaptations in electromyographic, muscle fibre and force production characteristics of human leg extensor muscles with special reference to prolonged heavy resistance and explosive type strength training. 106 p. 1986.
21 LAHTINEN, ULLA, Begåvningshandikappad ungdom i utveckling. En uppföljningstudie av funktionsförmåga och fysisk aktivitet hos begåvningshandikappade ungdomar i olika livsmiljöer. 300 p. 1986.
22 SILVENNOINEN, MARTTI, Koululainen liikunnanharrastajana: liikuntaharrastusten ja liikuntamotiivien sekä näiden yhteyksien muuttuminen iän mukana peruskoululaisilla ja lukiolaisilla. - Schoolchildren and physically active interests: The changes in interests in and motives for physical exercise related to age in Finnish comprehensive and upper secondary schools. 226 p. 1987.
23 POHJOLAINEN, PERTTI, Toimintakykyisyys, terveydentila ja elämäntyyli 71-75-vuotiailla miehillä. - Functional capacity, health status and life-style among 71-75 year-old men. 249 p. Summary 13 p. 1987.
24 MERO, ANTTI, Electromyographic acticity, force and anaerobic energy production in sprint running; with special reference to different constant speeds ranging from submaximal to supramaximal. 112 p. Tiivistelmä 5 p. 1987.
25 PARKATTI, TERTTU, Self-rated and clinically measured functional capacity among women and men in two age groups in metal industry. 131 p. Tiivistelmä 2 p. 1990.
26 HOLOPAINEN, SINIKKA, Koululaisten liikuntataidot. - The motor skills of schoolboys and girls. 217 p. Summary 6 p. 1990.
27 NUMMINEN, PIRKKO, The role of imagery in physical education. 131 p. Tiivistelmä 10 p. 1991.
28 TALVITIE, ULLA, Aktiivisuuden ja omatoimivuuden kehittäminen fysioterapian tavoitteena. Kehittävän työntutkimuksen sovellus lääkintävoimistelijan työhön. - The development of activity and self-motivation as the aim of physiotherapy. The application of developmental work research in physiotherapy. 212 p. Summary 8 p. 1991.
29 KAHILA, SINIKKA, Opetusmenetelmän merkitys prososiaalisessa oppimisessa - auttamis-

käyttäytymisen edistäminen yhteistyöskentelyn avulla koululiikunnassa. - The role of teaching method in prosocial learning - developing helping behavior by means of the cooperative teaching method in physical education. 132 p. Summary 2 p. 1993.

30 LIIMATAINEN-LAMBERG, ANNA-ESTER, Changes in student smoking habits at the vocational institutions and senior secondary schools and health education. 195 p. Yhteenveto 5 p. 1993.

31 KESKINEN, KARI LASSE, Stroking characteristics of front crawl swimming. 77 p. Yhteenveto 2 p. 1993.

32 RANTANEN, TAINA, Maximal isometric strength in older adults. Cross-national comparisons, background factors and association with Mobility. 87 p. Yhteenveto 4 p. 1994.

33 LUSA, SIRPA, Job demands and assessment of the physical work capacity of fire fighters. 91 p. Yhteenveto 4 p. 1994.

34 CHENG, SULIN, Bone mineral density and quality in older people. A study in relation to exercise and fracture occurrence, and the assessment of mechanical properties. 81 p. Tiivistelmä 1 p. 1994.

35 KOSKI, PASI, Liikuntaseura toimintaympäristössään. - Sports club in its organizational environment. 220 p. Summary 6 p. 1994.

36 JUPPI, JOEL, Suomen julkinen liikuntapolitiikka valtionhallinnon näkökulmasta vuosina 1917-1994. - Public sport policy in Finland from the viewpoint of state administration in 1917-1994. 358 p. Summary 7 p. 1995.

37 KYRÖLÄINEN, HEIKKI, Neuromuscular performance among power- and endurance-trained athletes. 82 p. Tiivistelmä 3 p. 1995.

38 NYANDINDI, URSULINE S., Evaluation of a school oral health education programme in Tanzania: An ecological perspective. 88 p. Tiivistelmä 2 p. 1995.

39 HEIKINARO-JOHANSSON, PILVIKKI, Including students with special needs in physical education. 81 p. Yhteenveto 4 p. 1995.

40 SARLIN, EEVA-LIISA, Minäkokemuksen merkitys liikuntamotivaatiotekijänä. - The significance of self perception in the motivational orientation of physical education. 157 p. Summary 4 p. 1995.

41 LINTUNEN, TARU, Self-perceptions, fitness, and exercise in early adolescence: a four-year follow-up study. 87 p. Yhteenveto 5 p.1995.

42 SIPILÄ, SARIANNA, Physical training and skeletal muscle in elderly women. A study of muscle mass, composition, fiber characteristics and isometric strength. 62 p. Tiivistelmä 3 p. 1996.

43 ILMANEN, KALERVO, Kunnat liikkeellä. Kunnallinen liikuntahallinto suomalaisen yhteiskunnan muutoksessa 1919-1994. - Municipalities in motion. Municipal sport administration in the changing Finnish society 1919-1994. 285 p. Summary 3 p. 1996.

44 NUMMELA, ARI, A new laboratory test method for estimating anaerobic performance characteristics with special reference to sprint running. 80 p. Yhteenveto 4 p. 1996.

45 VARSTALA, VÄINÖ, Opettajan toiminta ja oppilaiden liikunta-aktiivisuus koulun liikuntatunnilla. - Teacher behaviour and students' motor engagement time in school physical education classes. 138 p. Summary 4 p. 1996.

46 POSKIPARTA, MARITA, Terveysneuvonta, oppimaan oppimista. Videotallenteet hoitajien terveysneuvonnan ilmentäjinä ja vuorovaikutustaitojen kehittämismenetelmänä. - Health counselling, learning to learn. Videotapes expressing and developing nurses´ communication skills. 159 p. Summary 6 p. 1997.

47 SIMONEN, RIITTA, Determinants of adult psychomotor speed. A study of monozygotic twins. - Psykomotorisen nopeuden determinantit identtisillä kaksosilla. 49 p. Yhteenveto 2 p. 1997.

48 NEVALA-PURANEN, NINA, Physical work and ergonomics in dairy farming. Effects of occupationally oriented medical rehabilitaton and environmental measures. 80 p. (132 p.) 1997.

49 HEINONEN, ARI, Exercise as an Osteogenic Stimulus. 69 p. (160 p.) Tiivistelmä 1 p. 1997.

50 VUOLLE, PAULI (Ed.) Sport in social context by Kalevi Heinilä. Commemorative book in Honour of Professor Kalevi Heinilä. 200 p. 1997.

51 TUOMI, JOUNI, Suomalainen hoitotiedekeskustelu. - The genesis of nursing and caring science in Finland. 218 p. Summary 7 p. 1997.

52 TOLVANEN, KAIJA, Terveyttä edistävän organisaation kehittäminen oppivaksi organisaatioksi. Kehitysnäytökset ja kehittämistehtävät terveyskeskuksen muutoksen virittäjänä. - Application of a learning organisation model to improve services in a community health centre. Development examples and development tasks are the key to converting a health care. 197 p. Summary 3 p. 1998.

53 OKSA, JUHA, Cooling and neuromuscular performance in man. 61 p. (121 p.) Yhteenveto 2 p. 1998.

54 GIBBONS, LAURA, Back function testing and paraspinal muscle magnetic resonance image parameters: their associations and determinants. A study on male, monozygotic twins. 67 p (128 p.) Yhteenveto 1p. 1998.

55 NIEMINEN, PIPSA, Four dances subcultures. A study of non-professional dancers´ socialization, participation motives, attitudes and stereotypes. - Neljä tanssin alakulttuuria. Tutkimus tanssinharrastajien tanssiin sosiaalistumisesta, osallistumismotiiveista, asenteista ja stereotypioista. 165 p. Yhteenveto 4 p. 1998.

56 LAUKKANEN, PIA, Iäkkäiden henkilöiden selviytyminen päivittäisistä toiminnoista. - Carrying

out the activities of daily living among elderly people. 130 p. (189 p.). Summary 3 p. 1998.

57 AVELA, JANNE, Stretch-reflex adaptation in man. Interaction between load, fatigue and muscle stiffness. 87 p. Yhteenveto 3 p. 1998.

58 SUOMI, KIMMO, Liikunnan yhteissuunnittelumetodi. Metodin toimivuuden arviointi Jyväskylän Huhtasuon lähiössä. - Collaborative planning method of sports culture. Evaluation of the method in the Huhtasuo suburb of the city of Jyväskylä. 190 p. Summary 8 p. 1998.

59 PÖTSÖNEN, RIIKKA, Naiseksi, mieheksi, tietoiseksi. Koululaisten seksuaalinen kokeneisuus, HIV/AIDS-tiedot, -asenteet ja tiedonlähteet. - Growing as a woman, growing as a man, growing as a conscious citizen. 93 p. (171 p.). Summary 3 p. 1998.

60 HÄKKINEN, ARJA, Resistance training in patients with early inflammatory rheumatic diseases. Special reference to neuromuscular function, bone mineral density and disease activity. - Dynaamisen voimaharjoittelun vaikutukset nivelreumaa sairastavien potilaiden lihasvoimaan, luutiheyteen ja taudin aktiivisuuteen. 62 p. (119 p.) Yhteenveto 1 p. 1999.

61 TYNJÄLÄ, JORMA, Sleep habits, perceived sleep quality and tiredness among adolescents. A health behavioural approach. - Nuorten nukkumistottumukset, koettu unen laatu ja väsyneisyys. 104 p. (167 p.) Yhteenveto 3 p. 1999.

62 PÖNKKÖ, ANNELI, Vanhemmat ja lastentarhanopettajat päiväkotilasten minäkäsityksen tukena. - Parents´ and teachers´ role in self-perception of children in kindergartens. 138 p. Summary 4 p. 1999.

63 PAAVOLAINEN, LEENA, Neuromuscular characteristics and muscle power as determinants of running performance in endurance athletes with special reference to explosive-strength training. - Hermolihasjärjestelmän toimintakapasiteetti kestävyyssuorituskykyä rajoittavana tekijänä. 88 p. (138 p.) Yhteenveto 4 p. 1999.

64 VIRTANEN, PAULA, Effects of physical activity and experimental diabetes on carbonic anhydrace III and markers of collagen synthesis in skeletal muscle and serum. 77 p. (123 p.) Yhteenveto 2 p. 1999.

65 KEPLER, KAILI, Nuorten koettu terveys, terveyskäyttäytyminen ja sosiaalistumisympäristö Virossa. - Adolescents' perceived health, health behaviour and socialisation enviroment in Estonia. - Eesti noorte tervis, tervisekäitumine ja sotsiaalne keskkond. 203 p. Summary 4p. Kokkuvõte 4 p. 1999.

66 SUNI, JAANA, Health-related fitness test battery for middle-aged adults with emphasis on musculoskeletal and motor tests. 96 p. (165 p.) Yhteenveto 2 p. 2000.

67 SYRJÄ, PASI, Performance-related emotions in highly skilled soccer players. A longitudinal study based on the IZOF model. 158 p. Summary 3 p. 2000.

68 VÄLIMAA, RAILI, Nuorten koettu terveys kyselyaineistojen ja ryhmähaastattelujen valossa. - Adolescents' perceived health based on surveys and focus group discussions. 208 p. Summary 4 p. 2000.

69 KETTUNEN, JYRKI, Physical loading and later lower-limb function and findings . A study among male former elite athletes. - Fyysisen kuormituksen yhteydet alaraajojen toimintaan ja löydöksiin entisillä huippu-urhelijamiehillä. 68 p. (108 p.) Yhteenveto 2 p. 2000.

70 HORITA, TOMOKI, Stiffness regulation during stretch-shortening cycle exercise. 82 p. (170 p.) 2000.

71 HELIN, SATU, Iäkkäiden henkilöiden toimintakyvyn heikkeneminen ja sen kompensaatioprosessi. - Functional decline and the process of compensation in elderly people. 226 p. Summary 10 p. 2000.

72 KUUKKANEN, TIINA, Therapeutic exercise programs and subjects with low back pain. A controlled study of changes in function, activity and participation. 92 p. (154 p.) Tiivistelmä 2 p. 2000.

73 VIRMAVIRTA, MIKKO, Limiting factors in ski jumping take-off. 64 p. (124 p.) Yhteenveto 2 p. 2000.

74 PELTOKALLIO, LIISA, Nyt olisi pysähtymisen paikka. Fysioterapian opettajien työhön liittyviä kokemuksia terveysalan ammatillisessa koulutuksessa. - Now it's time to stop. Physiotherapy teachers' work experiences in vocational health care education. 162 p. Summary 5 p. 2001.

75 KETTUNEN, TARJA, Neuvontakeskustelu. Tutkimus potilaan osallistumisesta ja sen tukemisesta sairaalan terveysneuvonnassa. - Health counseling conversation. A study of patient participation and its support by nurses during hospital counseling. 123 p. (222 p.) Summary 6 p. 2001.

76 PULLINEN, TEEMU, Sympathoadrenal response to resistance exercise in men, women and pubescent boys. With special reference to interaction with other hormones and neuromuscular performance. 76 p. (141 p.) Yhteenveto 2 p. 2001.

77 BLOMQVIST, MINNA, Game understanding and game performance in badminton. Development and validation of assessment instruments and their application to games teaching and coaching. 83 p. Yhteenveto 5 p. 2001.

78 FINNI, TAIJA, Muscle mechanics during human movement revealed by *in vivo* measurements of tendon force and muscle length. 83 p. (161 p.) Yhteenveto 3 p. 2001.

79 KARIMÄKI, ARI, Sosiaalisten vaikutusten arviointi liikuntarakentamisessa. Esimerkkinä Äänekosken uimahalli. - Social impact

assessment method in sports planning. - The case of Äänekoski leisure pool. 194 p. Summary 3 p. 2001.

80 PELTONEN, JUHA, Effects of oxygen fraction in inspired air on cardiorespiratory responses and exercise performance. 86 p. (126 p.) Yhteenveto 2 p. 2002.

81 HEINILÄ, LIISA, Analysis of interaction processes in physical education. Development of an observation instrument, its application to teacher training and program evaluation. 406 p. Yhteenveto 11 p. 2002.

82 LINNAMO, VESA, Motor unit activation and force production during eccentric, concentric and isometric actions. - Motoristen yksiköiden aktivointi ja lihasten voimantuotto eksentrisessä, konsentrisessa ja isometrisessä lihastyössä. 77 p. (150 p.) Yhteenveto 2 p. 2002.

83 PERTTUNEN, JARMO, Foot loading in normal and pathological walking. 86 p. (213 p.) Yhteenveto 2 p. 2002.

84 LEINONEN, RAIJA, Self-rated health in old age. A follow-up study of changes and determinants. 65 p. (122 p.) Yhteenveto 2 p. 2002.

85 GRETSCHEL, ANU, Kunta nuorten osallisuusympäristönä. Nuorten ryhmän ja kunnan vuorovaikutussuhteen tarkastelu kolmen liikuntarakentamisprojektin laadunarvioinnin keinoin. - The municipality as an involvement environment - an examination of the interactive relationship between youth groups and municipalities through the quality assessment of three sports facilities construction projects. 236 p. Summary 11 p. 2002.

86 PÖYHÖNEN, TAPANI, Neuromuscular function during knee exercises in water. With special reference to hydrodynamics and therapy. 77 p. (124 p.) Yhteenveto 2 p. 2002.

87 HIRVENSALO, MIRJA, Liikuntaharrastus iäkkäänä. Yhteys kuolleisuuteen ja avuntarpeeseen sekä terveydenhuolto liikunnan edistäjänä. - Physical activity in old age - significance for public health and promotion strategies. 106 p. (196 p.) Summary 4 p. 2002.

88 KONTULAINEN, SAIJA, Training, detraining and bone - Effect of exercise on bone mass and structure with special reference to maintenance of exercise induced bone gain. 70 p. (117 p.) Yhteenveto 2 p. 2002.

89 PITKÄNEN, HANNU, Amino acid metabolism in athletes and non-athletes. - With Special reference to amino acid concentrations and protein balance in exercise, training and aging. 78 p. (167 p.) Yhteenveto 3 p. 2002.

90 LIIMATAINEN, LEENA, Kokemuksellisen oppimisen kautta kohti terveyden edistämisen asiantuntijuutta. Hoitotyön ammattikorkeakouluopiskelijoiden terveyden edistämisen oppiminen hoitotyön harjoittelussa. - Towards health promotion expertise through experiential learning. Student nurses' health promotion learning during clinical practice. 93 p. (164 p.) Summary 4 p. 2002.

91 STÅHL, TIMO, Liikunnan toimintapolitiikan arviointia terveyden edistämisen kontekstissa. Sosiaalisen tuen, fyysisen ympäristön ja poliittisen ympäristön yhteys liikunta-aktiivisuuteen. - Evaluation of the Finnish sport policy in the context of health promotion. Relationships between social support, physical environment, policy environment and physical activity 102 p. (152 p.) Summary 3 p. 2003.

92 OGISO, KAZUYUKI, Stretch Reflex Modulation during Exercise and Fatigue. 88 p. (170 p.) Yhteenveto 1 p. 2003.

93 RAUHASALO, ANNELI, Hoitoaika lyhenee – koti kutsuu. Lyhythoitoinen kirurginen toiminta vanhusten itsensä kokemana. - Care-time shortens – home beckons. Short term surgical procedures as experienced by elderly patients. 194 p. Summary 12 p. 2003.

94 PALOMÄKI, SIRKKA-LIISA, Suhde vanhenemiseen. Iäkkäät naiset elämänsä kertojina ja rakentajina. - Relation to aging. Elderly women as narrators and constructors of their lives. 143 p. Summary 6 p. 2004.

95 SALMIKANGAS, ANNA-KATRIINA, Nakertamisesta hanketoimintaan. Tapaustutkimus Nakertaja-Hetteenmäen asuinalueen kehittämistoiminnasta ja liikunnan osuudesta yhteissuunnittelussa. - From togetherness to project activity. A case study on the development of a neighbourhood in Kainuu and the role of physical activity in joint planning. 269 p. Summary 8 p. 2004.

96 YLÖNEN, MAARIT E., Sanaton dialogi. Tanssi ruumiillisena tietona. - Dialogue without words. Dance as bodily knowledge. 45 p. (135 p.) Summary 5 p. 2004.

97 TUMMAVUORI, MARGAREETTA, Long-term effects of physical training on cardiac function and structure in adolescent cross-country skiers. A 6.5-year longitudinal echocardiographic study. 151 p. Summary 1 p. 2004.

98 SIROLA, KIRSI, Porilaisten yhdeksäsluokkalaisten ja kasvattajien käsityksiä nuorten alkoholinkäytöstä ja alkoholinkäytön ehkäisystä. - Views of ninth graders, educators and parents in Pori, Finland on adolescent alcohol use and on preventing alcohol use. 189 p. Summary 3 p. 2004.

99 LAMPINEN, PÄIVI, Fyysinen aktiivisuus, harrastustoiminta ja liikkumiskyky iäkkäiden ihmisten psyykkisen hyvinvoinnin ennustajina. 65–84-vuotiaiden jyväskyläläisten 8-vuotisseuruututkimus. - Activity and mobility as associates and predictors of mental well-being among older adults. 94 p. (165 p.) Summary 2 p. 2004.

100 RANTA, SARI, Vanhenemismuutosten eteneminen. 75-vuotiaiden henkilöiden antropometristen ominaisuuksien, fyysisen toimintakyvyn ja kognitiivisen kyvykkyyden muutokset viiden ja kymmenen vuoden seuranta-aikana. - The progress of aging processes. A 5- and 10-year follow-up study of the changes in anthropometrical characteristics and physical and cognitive capacities among 75-year-old persons. 186 p. Summary 2 p. 2004.

101 SIHVONEN, SANNA, Postural balance and aging. Cross-sectional comparative studies and a balance training intervention. - Ikääntyminen ja tasapaino. Eri ikäisten tasapaino ja tasapainoharjoittelun vaikuttavuus ikääntyneillä palvelukodissa asuvilla naisilla. 65 p. (106 p.) Yhteenveto 2 p. 2004.

102 RISSANEN, AARO, Back muscles and intensive rehabilitation of patients with chronic low back pain. Effects on back muscle structure and function and patient disability. - Selkälihakset ja pitkäaikaista selkäkipua sairastavien potilaiden intensiivinen kuntoutus. Vaikutukset selkälihasten rakenteeseen ja toimintaan sekä potilaiden vajaakuntoisuuteen. 90 p. (124 p.) Yhteenveto 2 p. 2004.

103 KALLINEN, MAURI, Cardiovascular benefits and potential hazards of physical exercise in elderly people. - Liikunnan hyödylliset ja mahdolliset haitalliset vaikutukset ikääntyneiden verenkiertoelimistöön. 97 p. (135 p). Yhteenveto 2 p. 2004.

104 SÄÄKSLAHTI, ARJA, Liikuntaintervention vaikutus 3–7-vuotiaiden lasten fyysiseen aktiivisuuteen ja motorisiin taitoihin sekä fyysisen aktiivisuuden yhteys sydän- ja verisuonitautien riskitekijöihin. - Effects of physical activity Intervention on physical activity and motor skills and relationships between physical activity and coronary heart disease risk factors in 3–7-year-old children. 153 p. Summary 3 p. 2005.

105 HÄMÄLÄINEN, PIIA, Oral health status as a predictor of changes in general health among elderly people. 76 p. (120 p.) Summary 2 p. 2005.

106 LIINAMO, ARJA, Suomalaisnuorten seksuaalikasvatus ja seksuaaliterveystiedot oppilaan ja koulun näkökulmasta. Arviointia terveyden edistämisen viitekehyksessä. - Sexual education and sexual health knowledge among Finnish adolescents at pupil and school level. Evaluation from the point of view of health promotion. 111 p. (176 p.) Summary 5 p. 2005.

107 ISHIKAWA, MASAKI, *In vivo* muscle mechanics during human locomotion. Fascicle-tendinous tissue interaction during stretch-shortening cycle exercises. - Venytysrefleksin muutokset liikkeessä ja väsymyksessä. 89 p. (228 p.) Yhteenveto 1 p. 2005.

108 KÄRKI, ANNE, Physiotherapy for the functioning of breast cancer patients. Studies of the effectiveness of physiotherapy methods and exercise, of the content and timing of post-operative education and of the experienced functioning and disability . - Rintasyöpäleikattujen toimintakyky ja siihen vaikuttaminen fysioterapiassa ja harjoittelussa. 70 p. (138 p.) Yhteenveto 3 p. 2005.

109 RAJANIEMI, VESA, Liikuntapaikkarakentaminen ja maankäytön suunnittelu. Tutkimus eri väestöryhmät tasapuolisesti huomioon ottavasta liikuntapaikkasuunnittelusta ja sen kytkemisestä maankäyttö- ja rakennuslain mukaiseen kaavoitukseen. - Sports area construction and land use planning – Study of sports area planning that considers all the population groups even-handedly and integrates sports area planning with land use planning under the land use and building act. 171 p. Summary 6 p. 2005.

110 WANG, QINGJU, Bone growth in pubertal girls. Cross-sectional and lingitudinal investigation of the association of sex hormones, physical activity, body composition and muscle strength with bone mass and geometry. 75 p. (117 p.) Tiivistelmä 1 p. 2005.

111 ROPPONEN, ANNINA, The role of heredity, other constitutional structural and behavioral factors in back function tests.- Perimä, muut synnynnäiset rakenteelliset tekijät ja käyttäytymistekijät selän toimintakykytesteissä. 78 P. (125 p.) Tiivistelmä 1 p. 2006.

112 ARKELA-KAUTIAINEN, MARJA, Functioning and quality of life as perspectives of health in patients with juvenile idiopathic arthritis in early adulthood. Measurement and long-term outcome. - Toimintakyky ja elämänlaatu terveyden näkökulmina lastenreumaa sairastaneilla nuorilla aikuisilla. Mittaaminen ja pitkäaikaistulokset. 95 p. (134 p.) Tiivistelmä 2 p. 2006.

113 RAUTIO, NINA, Seuruu- ja vertailututkimus sosioekonomisen aseman yhteydestä toimintakykyyn iäkkäillä henkilöillä. - A follow-up and cross-country comparison study on socio-economic position and its relationship to functional capacity in elderly people. 114 p. (187 p.) Summary 3 p. 2006.

114 TIIKKAINEN, PIRJO, Vanhuusiän yksinäisyys. Seuruutukimus emotionaalista ja sosiaalista yksinäisyyttä määrittävistä tekijöistä. - Loneliness in old age – a follow-up study of determinants of emotional and social loneliness. 76 p. (128 p.) Summary 2 p. 2006.

115 AHTIAINEN, JUHA, Neuromuscular, hormonal and molecular responses to heavy resistance training in strength trained men; with special reference to various resistance exercise protocols, serum hormones and gene expression of androgen receptor and insulin-like growth factor-I. - Neuromuskulaariset,

hormonaaliset ja molekulaariset vasteet voimaharjoittelussa voimaurheilijoilla. 119 p. (204 p.) Yhteenveto 2 p. 2006.

116 Pajala, Satu, Postural balance and susceptibility to falls in older women. Genetic and environmental influences in single and dual task situations. - Iäkkäiden naisten tasapainokyky yksinkertaisissa sekä huomion jakamista vaativissa tilanteissa ja kaatumisriskiperimän merkitys yksilöiden välisten erojen selittäjinä. 78 p. (120 p.) Yhteenveto 3 p. 2006.

117 Tiainen, Kristina, Genetics of skeletal muscle characteristics and maximal walking speed among older female twins. - Lihasvoiman ja kävelynopeuden periytyvyys iäkkäillä naiskaksosilla. 77 p. (123 p.) Yhteenveto 2 p. 2006.

118 Sjögren, Tuulikki, Effectiveness of a workplace physical exercise intervention on the functioning, work ability, and subjective well-being of office workers – a cluster randomised controlled cross-over trial with one-year follow-up. - Työpaikalla tapahtuvan fyysisen harjoitteluintervention vaikuttavuus toimistotyöntekijöiden toimintakykyyn, työkykyyn ja yleiseen subjektiiviseen elämänlaatuun – ryhmätasolla satunnaistettu vaihtovuorokoe ja vuoden seuranta. 100 p. (139 p.) Tiivistelmä 3 p. 2006.

119 Lyyra, Tiina-Mari, Predictors of mortality in old age. Contribution of self-rated health, physical functions, life satisfaction and social support on survival among older people. - Kuolleisuuden ennustetekijät iäkkäässä väestössä. Itsearvioidun terveyden, fyysisten toimintojen, elämään tyytyväisyyden ja sosiaalisen tuen yhteys iäkkäiden ihmisten eloonjäämiseen. 72 p. (106 p.) Tiivistelmä 2 p. 2006.

120 Soini, Markus, Motivaatioilmaston yhteys yhdeksäsluokkalaisten fyysiseen aktiivisuuteen ja viihtymiseen koulun liikuntatunneilla. - The relationship of motivational climate to physical activity intensity and enjoyment within ninth grade pupils in school physical education lessons. 91 p. 2006.

121 Vuorimaa, Timo, Neuromuscular, hormonal and oxidative stress responses to endurance running exercises in well trained runners. - Neuromuskulaariset, hormonaaliset ja hapettumisstressiin liittyvät vasteet kestävyysjuoksuharjoituksiin hyvin harjoitelleilla juoksijoilla. 93 p. (152 p.) Yhteenveto 3 p. 2007.

122 Mononen, Kaisu, The effects of augmented feedback on motor skill learning in shooting. A feedback training intervention among inexperienced rifle shooters. - Ulkoisen palautteen vaikutus motoriseen oppimiseen ammunnassa: Harjoittelututkimus kokemattomilla kivääriampujilla. 63 p. Yhteenveto 4 p. 2007.

123 Sallinen, Janne, Dietary Intake and Strength Training Adaptation in 50–70 -year old Men and Women. With special reference to muscle mass, strength, serum anabolic hormone concentrations, blood pressure, blood lipids and lipoproteins and glycemic control. - Ravinnon merkitys voimaharjoittelussa 50–70 -vuotiailla miehillä ja naisilla 103 p. (204 p.) Yhteenveto 3 p. 2007.

124 Kasila Kirsti, Schoolchildren's oral health counselling within the organisational context of public oral health care. Applying and developing theoretical and empirical perspectives. 96 p. (139 p.) Tiivistelmä 3 p. 2007.

125 Pyöriä, Outi, Reliable clinical assessment of stroke patients' postural control and development of physiotherapy in stroke rehabilitation. - Aivoverenkiertohäiriöpotilaiden toimintakyvyn luotettava kliininen mittaaminen ja fysioterapian kehittäminen Itä-Savon sairaanhoitopiirin alueella. 94 p. (143 p.) Yhteenveto 6 p. 2007.

126 Valkeinen, Heli, Physical fitness, pain and fatigue in postmenopausal women with fibromyalgia. Effects of strength training. - Fyysinen kunto, kipu- ja väsymysoireet ja säännöllisen voimaharjoittelun vaikutukset menopaussi-iän ohittaneilla fibromyalgiaa sairastavilla naisilla. 101 p. (132 p.) Yhteenveto 2 p. 2007.

127 Hämäläinen, Kirsi, Urheilija ja valmentaja urheilun maailmassa. Eetokset, ihanteet ja kasvatus urheilijoiden tarinoissa. - An athlete and a coach in the world of sports. Ethos, ideals and education in athletes' narratives. 176 p. Tiivistelmä 2 p. 2008.

128 Aittasalo, Minna, Promoting physical activity of working aged adults with selected personal approaches in primary health care. Feasibility, effectiveness and an example of nationwide dissemination. - Työikäisten liikunnan edistäminen avoterveydenhuollossa – työtapojen toteuttamiskelpoisuus ja vaikuttavuus sekä esimerkki yhden työtavan levittämisestä käytäntöön. 105 p. (161 p.) Yhteenveto 3 p. 2008.

129 Portegijs, Erja, Asymmetrical lower-limb muscle strength deficit in older people. - Alaraajojen lihasvoiman puoliero iäkkäillä ihmisillä. 105 p. (155 p.) Yhteenveto 3 p. 2008.

130 Laitinen-Väänänen, Sirpa, The construction of supervision and physiotherapy expertise: A qualitative study of physiotherapy students' learning sessions in clinical education. - Opiskelijan ohjauksen ja fysioterapian asiantuntijuuden rakentuminen: Laadullinen tutkimus fysioterapiaopiskelijan oppimistilanteista työharjoittelussa. 69 p. (118 p.) Yhteenveto 3 p. 2008.

131 Iivonen, Susanna, Early Steps -liikunta-ohjelman yhteydet 4–5-vuotiaiden päiväkotilasten motoristen perustaitojen kehitykseen. - The associations between an Early Steps physical education curriculum and the fundamental motor skills development of 4–5-year-old preschool children. 157 p. Summary 4 p. 2008.

132 Ortega-Alonso, Alfredo, Genetic effects on mobility, obesity and their association in older female twins. 87 p. 2009.

133 Hulmi, Juha, Molecular and hormonal responses and adaptation to resistance exercise and protein nutrition in young and older men. - Voimaharjoittelun fysiologiset ja molekyylibiologiset vaikutukset lihaskasvunsäätelyssä lisäproteiinia nautittaessa tai ilman. 109 p. (214 p.) Yhteenveto 2 p. 2009.

134 Martinmäki, Kaisu, Transient changes in heart rate variability in response to orthostatic task, endurance exercise and training. With special reference to autonomic blockades and time-frequency analysis. - Sykevaihtelun muutokset ortostaattisessa testissä, kestävyysliikunnassa ja kestävyysharjoittelussa käyttäen hyväksi autonomisen säätelyn salpauskokeita ja aika-taajuusanalyysiä . 99 p. (151 p.) Yhteenveto 2 p. 2009.

135 Sedliak, Milan, Neuromuscular and hormonal adaptations to resistance training. Special effects of time of day of training. 84 p. (175 p.) 2009.

136 Nikander, Riku, Exercise loading and bone structure. 97 p. (141 p.) Yhteenveto 1 p. 2009.

137 Korhonen, Marko T., Effects of aging and training on sprint performance, muscle structure and contractile function in athletes. - Ikääntymisen ja harjoittelun vaikutukset nopeussuorituskykyyn, lihasten rakenteeseen ja voimantuotto-ominaisuuksiin urheilijoilla. 123 p. (211 p.) Tiivistelmä 5 p. 2009.

138 Javanainen-Levonen, Tarja, Terveydenhoitajat liikunnanedistäjinä lastenneuvolatyössä. - Public Health Nurses as Physical Activity Promoters in Finnish Child Health Clinics. 104 p. (148 p.) Summary 6 p. 2009.

139 Klemola, Ulla, Opettajaksi opiskelevien vuorovaikutustaitojen kehittäminen liikunnan aineenopettajakoulutuksessa.- Developing student teachers´ social interaction skills in physical education teacher education. 92 p. (138 p.) Summary 4 p. 2009.

140 Niemi, Reetta, Onks tavallinen koe vai sellanen, missä pitää miettii? Ympäristölähtöisen terveyskasvatuspedagogiikan kehittäminen narratiivisena toimintatutkimuksena. - Is this a normal test or do we have to think? Developing environmentally oriented health education pedagogy through narrative action research . 215 p. 2009.

141 von Bonsdorff, Mikaela, Physical activity as a predictor of disability and social and health service use in older people. - Fyysinen aktiivisuus toiminnanvajauden ja sosiaali- ja terveyspalvelujen käytön ennustajana iäkkäillä henkilöillä 101 p. (134 p.) Yhteenveto 2 p. 2009.

142 Palomäki, Sanna, Opettajaksi opiskelevien pedagoginen ajattelu ja ammatillinen kehittyminen liikunnanopettajakoulutuksessa. - Pre-service teachers' pedagogical thinking and professional development in physical education teacher education. 118 p. (163 p.) Summary 3 p. 2009.

143 Vehmas, Hanna, Liikuntamatkalla Suomessa. Vapaa-ajan valintoja jälkimodernissa yhteiskunnassa. - Sport tourism in Finland – leisure choices in the post-modern society. 205 p. Summary 10 p. 2010.

144 Kokko, Sami, Health promoting sports club. Youth sports clubs' health promotion profiles, guidance, and associated coaching practice, in Finland. 147 p. (230 p.) Yhteenveto 5 p. 2010.

145 Kääriä, Sanna, Low back disorders in the long term among employees in the engineering industry. A study with 5-, 10- and 28-year follow-ups. - Metalliteollisuuden työntekijöiden alaselän sairaudet ikääntyessä: METELI–tutkimuksen 5–, 10– ja 28–vuotisseurantatutkimus. 76 p. (102 p.) Yhteenveto 2 p. 2010.

146 Santtila, Matti, Effects of added endurance or strength training on cardiovascular and neuromuscular performance of conscripts during the 8-week basic training period. - Lisätyn voima- ja kestävyysharjoittelun vaikutukset varusmiesten hengitys- ja verenkiertoelimistön sekä hermo-lihas järjestelmän suorituskykyyn kahdeksan viikon peruskoulutuskauden aikana. 85 p. (129 p.) Yhteenveto 2 p. 2010.

147 mänty, Minna, Early signs of mobility decline and physical activity counseling as a preventive intervention in older people. - Liikkumiskyvyn heikkenemistä ennakoivat merkit ja liikuntaneuvonta liikkumisvaikeuksien ehkäisyssä iäkkäillä henkilöillä. 103 p. (149 p.) Yhteenveto 2 p. 2010.

148 Rantalainen, Timo, Neuromuscular function and bone geometry and strength in aging. - Neuromuskulaarinen suorituskyky luun geometrian ja voiman selittäjänä ikääntymisen yhteydessä. 87 p. (120 p.) Yhteenveto 1 p. 2010.

149 Kuitunen, Sami, Muscle and joint stiffness regulation during normal and fatiguing stretch-shortening cycle exercise . - Lihas- ja niveljäykkyyden säätely normaalin sekä väsyttävän venymis-lyhenemissykli – tyyppisen harjoituksen aikana . 76 p. (142 p.) Yhteenveto 1 p. 2010.

150 Piitulainen, Harri, Functional adaptation of sarcolemma to physical stress. - Lihassolukalvon toiminnallinen mukautu minen fyysiseen kuormitukseen. 103 p. (178 p.) Yhteenveto 2 p. 2010.

151 Viljanen, Anne, Genetic and environmental effects on hearing acuity and the association between hearing acuity, mobility and falls in older women. - Kuulon tarkkuuden periytyvyys ja yhteys liikkumiskykyyn sekä kaatumisiin iäkkäillä naisilla. 85 p. (116 p.) Yhteenveto 2 p. 2010.

152 Kulmala, Jenni, Visual acuity in relation to functional performance, falls and mortality in old age. - Heikentyneen näöntarkkuuden vaikutus toimintakykyyn, kaatumisiin ja kuolleisuuteen iäkkäillä henkilöillä. 98 p. (140 p.) Yhteenveto 3 p. 2010.

153 Nivala, Sirkka, Kokemuksellinen vanheneminen sotainvalideilla. Suomalaisten sotainvalidien kokemus elämänkulustaan ja ikääntymisestään. - Disabled war veterans and experiential ageing. Finnish disabled war veterans and their experience of the course of their lives and growing older. 178 p. Summary 4 p. 2010.

154 Rinne, Marjo, Effects of physical activity, specific exercise and traumatic brain injury on motor abilities. Theoretical and pragmatic assessment. 86 p. (134 p.) Tiivistelmä 2 p. 2010.

155 Mikkola, Tuija, Genetic and environmental contributions to bone structural strength in postmenopausal women. - Perimän ja ympäristötekijöiden vaikutus luun lujuuteen vaihdevuosi-iän ohittaneilla naisilla. 77 p. (130 p.) Yhteenveto 2 p. 2010.

156 Salo, Petri, Assessing physical capacity, disability, and health-related quality of life in neck pain. 93 p. (132 p.) Yhteenveto 2 p. 2010.

157 Ronkainen, Paula, Towards powerful old age. Association between hormone replacement therapy and skeletal muscle. - Vaihdevuosioireisiin käytettävän HRT:n yhteys luurankolihaksiston rakenteeseen ja toimintaan. 118 p. (170 p.) Yhteenveto 2 p. 2010.

158 Kilpikoski, Sinikka, The McKenzie method in assessing, classifying and treating non-specific low back pain in adults with special reference to the centralization phenomenon. - McKenzien mekaaninen diagnostisointi- ja terapiamenetelmä tutkittaessa, luokiteltaessa ja hoidettaessa aikuisten epäspesifiä alaselkäkipua. 90 p. (130 p.) Yhteenveto 2 p. 2010.

159 Mutikainen, Sara, Genetic and environmental effects on resting electrocardiography and the association between electrocardiography and physical activity, walking endurance and mortality in older people. - Lepo-EKG –muuttujien periytyvyys sekä yhteydet fyysiseen aktiivisuuteen, kävelykestävyyteen ja kuolleisuuteen iäkkäillä henkilöillä. 84 p. (131 p.) Yhteenveto 3 p. 2010.

160 Völgyi, Eszter, Bone, fat and muscle gain in pubertal girls. Effects of physical activity. 76 p. (138 p.) Tiivistelmä 1 p. 2010.

161 Sillanpää, Elina, Adaptations in body composition, metabolic health and physical fitness during strength or endurance training or their combination in healthy middle-aged and older adults. 113 p. (179 p.) Yhteenveto 3 p. 2011.

162 Karavirta, Laura, Cardiorespiratory, neuromuscular and cardiac autonomic adaptations to combined endurance and strength training in ageing men and women. - Yhdistetyn kestävyys- ja voimaharjoittelun vaikutukset hengitys- ja verenkiertoelimistön sekä hermo-lihasjärjestelmän toimintaan ja sydämen autonomiseen säätelyyn ikääntyvillä miehillä ja naisilla. 108 p. (178 p.) Yhteenveto 2 p. 2011.

163 Hynynen, Esa, Heart rate variability in chronic and acute stress with special reference to nocturnal sleep and acute challenges after awakening. - Sykevariaatiomittaukset kroonisen ja akuutin stressin seurannassa käyttäen hyväksi yöunen ja akuuttien tehtävien aikaisia vasteita. 74 p. (109 p.) Yhteenveto 3 p. 2011.

164 Pavelka, Béla, Open Water as a Sportscape. Analysis of canoeing in Finland for developing sport infrastructure and services. 116 p. 2011.

165 Pesonen, Jyri, Opettajat oppijoina. Toiminta tutkimus liikunnanopettajien pätevöittämiskoulutuksen käynnistämisestä ja kehittämisesestä. - Teachers as learners – An action research on starting the development of qualifying training for teachers of physical education. 204 p. Summary 4 p. 2011.

166 Borremans, Erwin, Asperger syndrome and physical exercise. A study about sensomotor profiles, physical fitness, and the effectiveness of an exercise training program in a group of adolescents with Asperger syndrome. 111 p. (181 p.). Yhteenveto 3 p. 2011.

167 Ojala, Kristiina, Nuorten painon kokeminen ja laihduttaminen – Health Behaviour in School-aged Children (HBSC) study ja WHO-Koululaistutkimus. - Adolescents' self-perceived weight and weight reduction behaviour - Health Behaviour in School-aged Children (HBSC) study, a WHO Cross-National Survey. 151 p. (203 p.) Summary 4 p. 2011.

168 Rantakokko, Merja, Outdoor environment, mobility decline and quality of life among older people. - Ulkoympäristötekijät, ulkona liikkumisen heikkeneminen ja elämänlaatu iäkkäillä ihmisillä. 86 p. (119 p.) Yhteenveto 3 p. 2011.

169 Pöllänen, Eija, Regulation of gene expression and steroidogenesis in skeletal muscle of postmenopausal women - With emphasis on the effects of hormone replacement and power training. 114 p. (182 p.) Yhteenveto 2 p. 2011.

170 Yli-Piipari, Sami, The development of students' physical education motivation and physical activity. A 3.5-year longitudinal study across grades 6 to 9. - Koululaisten koululiikuntamotivaation ja fyysisen aktiivisuuden kehitys. 3.5 vuoden pitkittäistutkimus alakoulusta yläkouluun. 107 p. (218 p.) Yhteenveto 2 p. 2011.

171 Bottas, Reijo, Motor control of fast voluntary elbow movements. Exercise-induced muscle damage and soreness and learning interventions. - Kyynärvarren nopeiden tahdonalaisten liikkeiden motorinen kontrolli harjoituksessa aiheutetun lihassoluvaurion ja lihaskivun sekä oppimisen interventiona. 95 p. (206 p.) Yhteenveto 1 p. 2011.

172 Ma, Hongqiang, Adaptation of bone to physical activity and diet-induced obesity. - Luun mukautuminen fyysiseen aktiivisuuteen ja ravinnon aikaansaamaan lihavuuteen. 146 p. (197 p.) Yhteenveto 1 p. 2011.