JYU DISSERTATIONS 390

Tuuli Suominen

Adaptive Responses of Aging Bone to Physical Exercise

Masters Athletes and Patients with Hip Fracture as a Research Model

UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF SPORT AND
HEALTH SCIENCES

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Editors
Anne Viljanen
Faculty of Sport and Health Sciences, University of Jyväskylä
Päivi Vuorio
Open Science Centre, University of Jyväskylä

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ABSTRACT

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Physical function and physical loading, especially intensive osteogenic exercise, typically decrease with age, a phenomenon which likely contributes to age-related bone loss and a reduction in the osteogenic potential of exercise during aging. This study examined osteogenic responses to specific exercise among older adults representing the opposite ends of the physical function and bone health spectrum. Competitive male masters athletes aged 40-85 years participated in a randomized, controlled 20-week high-intensity strength and sprint training intervention (n=72) and in a 10-year follow-up (n=69). Men and women over age 60 years with a recent hip fracture (n=81) participated in a 12-month randomized controlled home-rehabilitation program. Tibial bone properties were assessed with peripheral quantitative computed tomography (pQCT). Physical function was measured with the Short Physical Performance Battery (SPPB) and perceived difficulty in walking outdoors, and lean body mass (LBM) was measured with a bioimpedance device. Compared to the athletes maintaining their usual sprint training schedules, the 20-week intensified strength and sprint training program improved the mid-tibial cross-sectional geometry and strength of the athletes in the intervention group. Strength and sprint training continued over 10 years was associated with maintained distal tibia bone mass, density and strength, and improved mid-tibia bone mass and geometry. In the less-trained athletes, who had reduced their training load, the corresponding bone properties declined during the follow-up. The home-based rehabilitation program had no effect on the tibial bone properties of the older adults with hip fracture as compared to those receiving standard care. Lower physical function and lower LBM were, however, predictive of greater deterioration in distal tibia bone traits during the first year post fracture. This research suggests that regular high-intensity exercise maintains the ability of a healthy aging bone structure to adapt to increased loading and counteracts age-related loss in bone cross-sectional geometry, density and strength. In aging people, a sufficient level of muscular capacity and physical function seem to be essential for bone maintenance across the physical activity and bone health spectrum.

Keywords: BMD, bone strength, hip fracture, masters athlete, high-impact training, strength training, home-exercise, rehabilitation, older adult

TIIVISTELMÄ (ABSTRACT IN FINNISH)

Suominen, Tuuli
Vanhenevan luuston vasteet liikuntaharjoitteluun: ikääntyvät urheilijat ja lonkkamurtumapotilaat tutkimusmallina
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Luusto heikkenee ikääntymisen myötä ja liikunnan luustovaikutukset ovat usein vaatimattomia. Alentunut fyysinen toimintakyky ja luuston vähäinen kuormitus saattavat osin selittää näitä ilmiöitä. Tämä tutkimus selvitti vanhenevan luuston mukautumiskykyä liikuntaan henkilöillä, jotka edustavat fyysisen toimintakyvyn ja luun terveyden ääripäitä. 40-85-vuotiaat pikajuoksijamiehet (n=72) osallistuivat 20 viikon satunnaistettuun, kontrolloituun voima- ja nopeusharjoittelututkimukseen ja 10-vuotisseurantaan (n=69). Yli 60-vuotiaat, lonkkamurtuman vuoksi äskettäin leikatut miehet ja naiset (n=81) osallistuivat 12 kuukauden satunnaistettuun, kontrolloituun kotikuntoutusohjelmaan. Sääriluun ominaisuuksia mitattiin perifeerisellä tietokonetomografialla (pQCT). Lonkkamurtumapotilaiden fyysistä toimintakykyä selvitettiin SPPB-testistöllä sekä koetuilla ulkona liikkumisen vaikeuksilla. Lihasmassaa mitattiin bioimpendanssilla mitatun rasvattoman kehonpainon avulla. 20 viikon tehostettu voima- ja pikajuoksuharjoittelu paransi urheilijoiden sääriluun varren geometrisia ominaisuuksia ja lujuutta verrattuna tavanomaista pikajuoksuharjoittelua jatkaneisiin urheilijoihin. Säännöllinen voima- ja pikajuoksuharjoittelu oli yhteydessä ylläpysyneeseen tai jopa parantuneeseen sääriluun varren poikkileikkausgeometriaan ja luumassaan, sekä ylläpysyneeseen sääriluun distaaliosan luumassaan, tiheyteen ja lujuuteen 10 vuoden seurannan aikana. Vuoden mittaisella kotikuntoutuksella ei ollut vaikutusta lonkkamurtumapotilaiden sääriluun ominaisuuksiin. Luun lujuusominaisuudet heikkenivät sekä kuntoutusryhmässä että tavanomaista hoitoa saaneessa verrokkiryhmässä. Murtuman jälkeinen heikompi toimintakyky ja alempi lihasmassa ennustivat sääriluun distaaliosan ominaisuuksien suurempaa heikkenemistä vuoden seurannan aikana. Tulosten mukaan intensiivinen, luita tehokkaasti kuormittava harjoittelu ylläpitää terveen luun mukautumiskykyä ja vastustaa ikääntymiseen liittyvää luuston heikkenemistä. Riittävä toimintakyky ja lihasten kunto ovat tärkeitä myös erityisen haurasluisten iäkkäiden henkilöiden, kuten lonkkamurtumapotilaiden luuston kunnon ylläpysymiselle.

Asiasanat: ikääntyminen, liikunta, luun lujuus, lonkkamurtuma, voimaharjoittelu, pikajuoksu, hyppelyharjoittelu, kotikuntoutus, keski-ikä, ikääntyneet, aikuisurheilu

Author

Tuuli Suominen, MSc
Gerontology Research Center
Faculty of Sport and Health Sciences
University of Jyväskylä
Finland
tuuli.suominen@jyu.fi
https://orcid.org/0000-0002-7270-6112

Supervisors

Professor Sarianna Sipilä, PhD
Gerontology Research Center
Faculty of Sport and Health Sciences
University of Jyväskylä
Finland

Researcher Marko Korhonen, PhD
Gerontology Research Center
Faculty of Sport and Health Sciences
University of Jyväskylä
Finland

Professor Ari Heinonen, PhD
Faculty of Sport and Health Sciences
University of Jyväskylä
Finland

Reviewers

Professor Saija Kontulainen, PhD
College of Kinesiology
University of Saskatchewan
Saskatoon, Canada

Associate Professor Maureen Ashe, PhD
Faculty of Medicine
University of British Columbia
Vancouver, Canada

Opponent

Senior Researcher Toni Rikkonen, PhD
Kuopio Musculoskeletal Research Unit
University of Eastern Finland
Kuopio, Finland

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FIGURES

TABLES

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to by their Roman numerals. (The thesis also includes unpublished data.)

I Suominen TH, Korhonen MT, Alén M, Heinonen A, Mero A, Törmäkangas T, Suominen H. 2017. Effects of a 20-week high-intensity strength and sprint training program on tibial bone structure and strength in middle-aged and older male sprint athletes: a randomized controlled trial. Osteoporosis International 28 (9): 2663-2673.

II Suominen TH, Alén M, Törmäkangas T, Degens H, Rittweger J, Heinonen A, Suominen H, Korhonen MT. Regular strength and sprint training counteracts bone aging: a 10-year follow-up in male masters athletes. 2021. JBMR Plus.
https://doi.org/10.1002/jbm4.10513

III Suominen TH, Edgren J, Salpakoski A, Arkela M, Kallinen M, Cervinka T, Rantalainen T, Törmäkangas T, Heinonen A, Sipilä S. 2019. Effects of a home-based physical rehabilitation program on tibial bone structure, density and strength after hip fracture: a secondary analysis of a randomized controlled trial. JBMR Plus 3 (6): e10175.
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IV Suominen TH, Edgren J, Salpakoski A, Kallinen M, Cervinka T, Rantalainen T, Törmäkangas T, Heinonen A, Sipilä S. 2020. Physical function and lean body mass as predictors of bone loss after hip fracture: a prospective follow-up study. BMC Musculoskeletal Disorders. 21: 367.
https://doi.org/10.1186/s12891-020-03401-3.

The author of this thesis was privileged to use pre-existing data in all studies. The author drafted the study questions and data analysis for the publications, quality checked and analyzed the bone scans, constructed the data files for statistical analysis, and performed the preliminary statistical analyses and part of the final analyses. A statistician was consulted on the more challenging statistical analyses. In addition, the author was mainly responsible for data interpretation, writing the manuscripts, and all steps in the publication process.

ABBREVIATIONS

25OHD	25-hydroxyvitamin D
A	anterior
A-L	anterolateral
A-M	anteromedial
ANOVA	analysis of variance
ATHLAS	Athlete Aging Study
BMC_{TOT}	total bone mineral content
BMI	body mass index
BMU	bone multicellular unit
BSI	compressive bone strength index
CSA_{CO}	cortical cross-sectional area
CSA_{CO}/CSA_{TOT}	ratio of cortical to total area
CSA_{TOT}	total cross-sectional area
CV	coefficient of variation
DXA	dual energy x-ray absorptiometry
ICD	international classification of disease
I_{maxA}	maximal area moment of inertia
I_{maxD}	density-weighted maximal moment of inertia
I_{minA}	minimal area moment of inertia
I_{minD}	density-weighted minimal moment of inertia
I_{polarA}	polar area moment of inertia
ITT	intention to treat
LBM	lean body mass
M	medial
MNAR	missing not at random
P	posterior
P-L	posterolateral
P-M	posteromedial
PP	per protocol
pQCT	peripheral quantitative computed tomography
ProMo	Promoting Mobility after Hip Fracture -study
PTH	parathyroid hormone
RCT	randomized controlled trial
SD	standard deviation
SE	standard error
SPPB	short physical performance battery
SSI	strength-strain index
Th_{CO}	cortical thickness
$vBMD_{CO}$	cortical volumetric bone mineral density
$vBMD_{TOT}$	total volumetric bone mineral density
$vBMD_{TRAB}$	trabecular volumetric bone mineral density

CONTENTS

1 INTRODUCTION

Bone mass and strength decline with aging. Physical activity, especially intensive bone loading exercise, also typically declines, a process that likely contributes to the age-related bone deterioration. Aging, when combined with physical inactivity and reduced bone strength, predisposes to osteoporosis, a disease characterized by enhanced bone fragility and increased fracture risk. Osteoporosis and related fragility fractures are a major public health problem, and the lifetime risk for an osteoporotic fracture is very high. Worldwide, every second woman and every fifth man aged 50 or older will sustain an osteoporotic fracture in their lifetime (Cauley & Giangregorio 2020). The total number of fractures is on the rise owing to the increase in the global elderly population (Kinsella & Wan 2009). Osteoporosis-related fractures impose substantial burdens in terms of costs, disability, pain, morbidity, and mortality (Cauley 2013). Hip fractures are particularly devastating in their impact on an individual's health and abilities.

Exercise is the only strategy that can simultaneously improve all modifiable factors for osteoporotic fractures, including bone strength and falls risk. While the osteogenic effects of exercise are most marked during youth, in adults exercise likely maintains bone or reduces bone deterioration rather than increases bone strength (Taaffe et al. 2013; Kontulainen & Johnston 2021). Older people have, however, been under-researched, especially in relation to the effects of exercise on bone geometric structure, which is another important contributor to bone strength besides bone density. Most previous studies have been conducted on relatively healthy, average, aging populations, leaving a knowledge gap on the effects of exercise on bone at both ends of the physical activity and bone health spectrum. The modesty or even absence of positive osteogenic effects of exercise among older people may, in part, be explained by reduced physical activity levels and low physical function that can limit one's ability to effectively load bones.

Masters athletes with a long history of high-intensity training may provide information on the osteogenic potential of vigorous bone-loading exercise during aging. At the same time, in athletes with already strong bone structures, further

adaptation may be minimal or even absent. While masters athletes do not represent typical older populations, they can serve as an ideal research model for studying age-related deterioration in bone and the effects of physical exercise on bone irrespective of confounding factors such as sedentary lifestyle and diseases (Lazarus & Harridge 2007).

The osteogenic potential of exercise among older people with low physical functioning and reduced bone strength has been little studied. Hip fracture is the most serious consequence of falls and osteoporosis, and it is followed by substantial and long-term deterioration of bone (Magaziner et al. 2006; Mikkola et al. 2007; Reider et al. 2010; Rathbun et al. 2016a; Rathbun et al. 2016b). When accompanied with the loss of physical function, bone deterioration increases the risk for a further hip or other osteoporotic fracture. Hence, it is important to minimize musculoskeletal losses after a hip fracture. The predictors of post-hip fracture bone loss remain understudied, and it is not known whether extremely fragile bones, such as those in patients with hip fracture, are able to adapt to increased loading. Moreover, most trials have focused on older adults who are, on average, considerably younger than people with hip fracture, while knowledge is also lacking on the osteogenic effects of exercise among the very elderly.

This doctoral dissertation examined the osteogenic potential and effects of exercise on bone cross-sectional geometry, density, and strength in older adults representing the less studied opposite poles of the physical activity, physical performance, and bone health spectrums: in middle-aged and older masters athletes with long training history, and in older people recovering from a hip fracture. In addition, the role of continued, intensive training on age-related bone deterioration, and the associations of physical function and muscle mass with post-fracture bone loss were examined. By combining and comparing the results of samples from the two extends, this dissertation extends our perspective on the adaptive capacity of aging bone and on the role of physical function and exercise in bone adaptation and maintenance during aging.

2 REVIEW OF THE LITERATURE

2.1 Bone structure and function

Bone is a complex and highly dynamic specialized connective tissue with several important functions. Bones provide a leverage system for locomotion and a frame for supporting the body. In addition, bones protect the internal organs and the spinal cord, help maintain mineral homeostasis, serve as an endocrine organ, and participate in hematopoiesis (Kartsogiannis & Ng 2004; Guntur & Rosen 2012). However, the primary function of bone is mechanical. To fulfill its mechanical roles, bone must be both stiff enough to endure high loads, flexible enough to absorb energy, and sufficiently light in weight to allow efficient locomotion. The unique composition and structure of bone enables these contrasting demands to be met (Fratzl et al. 2004; Seeman & Delmas 2006; Nair et al. 2013). In addition, bone must be adaptive enough to respond to changes in these demands and self-repair. The organization of bone is hierarchical and multidimensional, and bone properties from the macro-scale to nano-scale all contribute to its mechanical competence and function.

2.1.1 Composition of bone

Bone is a composite material made up of organic and inorganic phases. By weight, approximately 30% of bone tissue is organic matter, 60% is inorganic matter, and 10% is water (Morgan & Gerstenfeld 2020). The organic phase is composed predominantly of type I collagen and, to a minor extent, non-collagenous proteins. The inorganic phase is composed of bone mineral, impure hydroxyapatite, which is a naturally occurring calcium phosphate surrounding and filling the collagen fibrils. The collagen fibers are responsible for bone toughness i.e., absorb energy by deforming, whereas an increase in mineral

density increases stiffness but decreases elasticity (Fratzl et al. 2004; Seeman & Delmas 2006; Nair et al. 2013; Fonseca et al. 2014).

Bone cells constitute approximately 2% of the organic phase. There are four key cells that work in co-operation. Osteoblasts are responsible for the formation of new bone. They secrete the organic components of the bone extracellular matrix (osteoid), and regulate the mineralization of the matrix (Mackie 2003; Currey 2006, 11). Osteocytes are former osteoblasts embedded in the bone matrix. They form a network, which is visible as lacunae (small ellipsoidal cavities in bone matrix occupied by osteocyte cell bodies) and canaliculi (Schaffler et al. 2014). Osteocytes have a central role in regulating both bone formation and resorption by sensing and integrating mechanical and chemical signals from their environment (Schaffler et al. 2014). Osteoclasts are large, multinucleated cells responsible for bone resorption. They secrete acid and proteases to dissolve bone mineral and to destroy the organic matrix (Arnett 2013). Bone lining cells are also former osteoblasts and line the bone surface. Their purpose is thought to be that of coupling bone resorption and bone formation (Matsuo & Irie 2008).

2.1.2 Microstructure and macrostructure of bone

Microscopically, bone tissue presents in the form of primary or woven (immature) bone and secondary or lamellar (mature) bone. Immature, woven bone is characterized by a disorganized and spontaneous collagen arrangement, whereas in mature, lamellar bone, the collagen fibrils are laid down in a precise and deliberate lamellar pattern optimal for withstanding mechanical loads (Shapiro & Wu 2019; Hart et al. 2020). Lamellar bone presents as two macroscopic tissue types, cortical and trabecular bone, which are similar in their tissue composition but different in structure and function. Cortical, or compact bone accounts for approximately 80% of the entire adult skeletal mass (Fuchs, Thompson & Warden 2019). It forms the hard outer shell of bone and is at its most abundant in the diaphyseal, or shaft regions of the long bones where it forms a thick cortex surrounding the medullary canal. The cortex thins towards the bone ends, the metaphyseal and epiphyseal regions. The epiphysis is the rounded, expanded end of the long bone, whereas the metaphysis is a cone-shaped region between the epiphysis and diaphysis. The outer periosteal and inner endosteal surfaces of cortical bone are covered by sheets of special connective tissue (the periosteum and the endosteum) and layers of bone cells important for bone formation and adaptation (Seeman & Delmas 2006; Fuchs, Thompson & Warden 2019; Hart et al. 2020).

Cortical bone consists of parallel cylindrical columns known as osteons, or Haversian systems, which form its primary anatomical and functional units (Wittkowske et al. 2016). Each osteon contains several concentric lamellae of mineralized collagen fibers. These fibers surround the central longitudinal canal, the Haversian canal, which contains the blood and nerve supply. The collagen lamellae surrounding the Haversian canals are arranged in alternating parallel orientations forming a "twisted plywood-like" structure known to be highly fracture-resistant (Wittkowske et al. 2016). The dominant fiber orientation

usually follows the primary loading direction (Seto et al. 2008; Wittkowske et al. 2016). The highly organized and dense cortical type of bone is good in resisting sudden high loads (Hart et al. 2020). It has supportive, protective, and mechanical functions (Reeve 2017).

Trabecular or cancellous bone is located inside the cortical layer. It is found on flat and cuboidal bones such as vertebrae. In long bones, it is most abundant in the epiphyseal and metaphyseal regions. Trabecular bone consists of multiply connected, vertical and horizontal, rods and plates of bone called trabeculae, which are surrounded by bone marrow. Structurally, trabecular bone is highly porous and, compared to cortical bone, it has much a higher surface to volume ratio (Kenkre & Bassett 2018). Porosity in trabecular bone can range from 40% to 95% (due to the marrow spaces), whereas in cortical bone it is typically only 5-20% (mainly due to the canalicular and lacunar structures) (Morgan & Gerstenfeld 2020). While not as stiff as cortical bone, trabecular bone has the useful capability to evenly distribute mechanical load and absorb energy (Currey 2006, 146-173). Hence, it shows high resistance to cyclical low-grade forces (Hart et al. 2020). In addition, it has an important role in hematopoiesis and homeostasis (Fuchs, Thompson & Warden 2019).

2.1.3 Mechanical properties of bone

The mechanical properties of bone can be described with respect to its material (tissue-level) or its structural (whole bone-level) properties. The tissue level mechanical properties of bone are influenced by compositional factors such as mineral density and collagen content, and by other factors such as collagen fiber orientation and cross-linking, mineral crystal size and microstructure (van der Meulen, Jepsen & Mikić 2001; Fonseca et al. 2014). The structural properties of bone depend on both its material properties and geometry, such as size, shape, cortical thickness, cross-sectional area, and its trabecular architecture (Khan et al. 2001, 26).

The tissue-level (or whole bone-level) mechanical properties of bone can be determined in vitro by loading a bone tissue specimen (or whole bone) until failure (Turner & Burr 1993; Martin et al. 2015, 355-422). The behavior of a material (or structure) is represented in a stress-strain (or load-deformation) curve, which describes the deformation that the material (or structure) undergoes when subjected to a given load (Figure 1). Stress is the internal force generated in the bone sample that resists the external force. It is defined as the force applied per area unit and expressed in Newtons per square meter (N/m^2) (Currey 2006, 31-35). Strain, in turn, describes the deformation of the material, i.e., the change in length over original length (Currey 2006, 29). Strength is the amount of stress that the material (or structure) resists before permanent deformation or failure occurs, whereas stiffness indicates the ability to resist deformation under applied force. Although stiffness (mineral density) is essential for withstanding and transmitting loads, bone cannot be too stiff as energy absorption by deformation (toughness resilience by collagen) is also important in preventing structural failure (Seeman & Delmas 2006).

The linear part of the stress-strain curve reflects the intrinsic stiffness of the material (defined as stress/strain): the steeper the curve, the stiffer the material. The elastic region beneath the yield point reflects the ability of the material to elastically store energy and return to its original pre-deformation shape. In the plastic region after the yield point, the deformation is no longer proportional to the load, and permanent material damage, usually micro-damage begins. Tough materials show reasonable amount of post-yield deformation, i.e., absorb a lot of energy before breaking, whereas brittle materials break without any irrecoverable deformation (Currey 2006, 36). The stress-strain characteristics of trabecular and cortical bone differ markedly. Compared to cortical bone, the yield point for trabecular bone is lower and the plastic phase is longer, which indicates lower resistance to stress and higher resistance to strain (Hart et al. 2017).

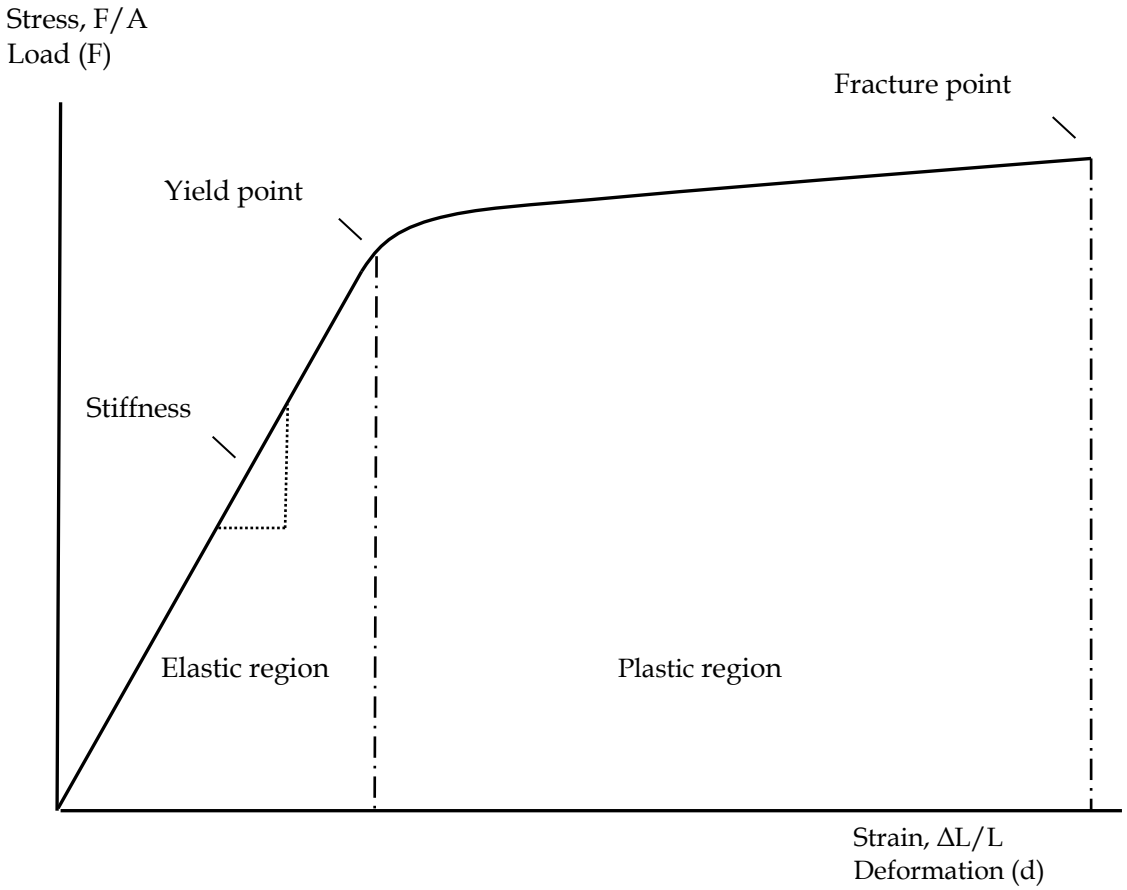

FIGURE 1 Schematic illustration of a stress-strain (load-deformation) curve. (F = force, A = area, L = length).

Physical forces produce stresses that can be classified as tensile, compressive or shear. Bones are usually weak in shear and stronger in compression than tension (Currey 2006, 41). Long bones are curved along their length, and hence subjected to combined axial compression and bending loading. In bending, the convex surface of the bone is in tension and the concave surface is in compression,

whereas in torsion, shear stresses are produced along the length of the bone (Khan et al. 2001, 31). These stresses acting on bones produce complex loading patterns, and hence their resistance to bending and torsion is essential.

In long bones, their tubular shape provides the least mass and the greatest strength during torsional and bending loading. Cross-sectional or area moment of inertia (CSMI or *I*) describes the capacity of a circular cross-section to resists bending and torsion. CSMI is given by $\frac{\pi}{4}(r_0^4 - r_1^4)$ where r_0 is the external radius and r_1 is the internal radius. Maximal CSMI is achieved when the bone material is distributed as far as possible from the neutral axis. Even a small increase in periosteal bone formation increases the CSMI considerably since the CSMI is proportional to the fourth power of the radius. However, with the same amount of material, the distance from the neutral axis cannot increase without limit as the bone eventually becomes too thin and susceptible to buckling (Currey 2006, 200). In bone, the mass around the neutral axis is asymmetrically distributed such that the diameter and thickness are higher in areas of high stress and lower in areas of low stress (Hart et al. 2017). The shape and size (inner and outer contours, dimensions, thickness, and diameter) of a bone thus reflect the complex loading patterns it is subjected to. The compressive and tensile strength of bone are directly proportional to its cross-sectional area (CSA) (Hart et al. 2017). Hence, both CSA and CSMI are important for load tolerability and fatigue resistance (Hart et al. 2017).

2.1.4 Modeling and remodeling

To achieve, maintain and alter its mechanical properties, bone must be highly adaptive and respond to changes in its environment. The cellular mechanisms responsible for bone adaptation are modeling and remodeling. Both processes optimize bone strength and minimize mass to achieve a strong yet lightweight structure (Seeman & Delmas 2006; Martin & Seeman 2008). Modeling, or construction, increases bone size and modifies bone shape through genetic regulation and in response to mechanical loading (Martin & Seeman 2008). In modeling, bone formation by osteoblasts or resorption by osteoclasts occurs independently on different bone surfaces (Szulc & Seeman 2009). Bone formation deposits new bone where it is needed, while bone resorption removes bone that is damaged or not adequately loaded. Modeling occurs mainly during growth; in adults, the rate and the extent of modeling are greatly reduced (Martin et al. 2015, 275-354). Examples of modeling during adulthood include slow, continuous periosteal and endocortical expansion (Seeman 2003).

Bone remodeling is a lifelong reconstruction process that adjusts the bone microstructure to meet changing mechanical needs, repairs microdamage, and prevents the accumulation of old, damaged bone (Frost 1997). Remodeling is performed by BMUs (bone multicellular units) and involves sequential bone resorption and bone formation of a comparable volume at the same spatial location. The remodeling cycle takes approximately 4-6 months and comprises three principal phases: activation, resorption and formation (Hadjidakis &

Androulakis 2006; Fuchs et al. 2008). Bone formation includes rapid primary mineralization of the new bone material whereas the completion of secondary mineralization takes many months or even years (Martin & Seeman 2008). As bone is initially replaced with less mineralized bone matrix, remodeling can result in increased porosity and decreased mineral density until secondary mineralization is complete (Heaney 1994).

2.2 Mechanoadaptation

The mechanical environment plays an essential role in the regulation of bone modeling and remodeling. *Mechanotransduction* refers to the multi-step process of transmitting and translating the initial mechanical signal into an actual biological effect (Duncan & Turner 1995). Current evidence based on in vitro bone cell models suggests that mechanical loading-induced interstitial fluid flow through the osteocyte lacuna-canalicula system, and the shear stresses induced by the fluid flow activate the cellular response (Schaffler et al. 2014; Wittkowske et al. 2016). *Mechanosensitivity* refers to mechanosensation, i.e., to the ability of bone tissue to detect mechanical signals. *Mechanoresponsiveness* describes the ability of bone to respond to changes in its mechanical environment.

2.2.1 Strain environment

As suggested by cell culture and animal studies, the adaptive response of bone to mechanical loading depends on a complex strain stimulus comprising several interlinked and interdependent aspects, including strain magnitude, strain frequency, strain rate, strain distribution, number of loading cycles and rest-recovery periods (Lanyon 1996; Hart et al. 2017). *Strain magnitude* is a key determinant of the adaptive response of bone (Rubin & Lanyon 1985; Hsieh et al. 2001). Frost's mechanostat theory (Frost 1987) proposes that minimum effective strain (MES) is necessary in order to maintain bone mass. Strain in excess of MES increases bone mass and strength. Conversely, a reduction in strain, such as occurs during disuse, rapidly compromises bone mass and strength. Disuse, maintenance and overload thresholds vary between bone sites according to their typical strain level (Hsieh et al. 2001). In addition, the thresholds appear to be genetically controlled and modified by several biochemical factors (Khan et al. 2001, 28).

Despite the importance of strain magnitude, large strains are not on their own enough to activate bone cells. Bone adaptation is driven by dynamic, cyclic loading rather than static loading (Lanyon & Rubin 1984; Turner 1998; Robling et al. 2002). The features of dynamic loading are strain frequency and strain rate, both of which seem to affect mechanotransduction by enhancing fluid flow within the bone tissue (Burr, Robling & Turner 2002; LaMothe, Hamilton & Zernicke 2005). *Strain frequency* denotes the number of strain events (cycles) per second whereas *strain rate* refers to the rate at which strain develops and is

released within each strain cycle (i.e., change in magnitude per second, or acceleration or deceleration of deformation). Strain frequency seems to affect mechanostat thresholds such that the adaptive response occurs at a lower strain magnitude as strain frequency increases (Hsieh & Turner 2001). At the same time, at an equivalent strain magnitude, bone formation is enhanced at higher loading frequencies (Hsieh et al. 2001). The response of bone to increased strain frequency is not, however, linear as at very high frequencies bone formation ceases altogether (Warden & Turner 2004).

Strain distribution denotes the way strain is distributed across a bone site. Since bone cells habituate to a customary loading environment, unusual strains of uneven distribution are required for effective bone adaptation (Lanyon 1996; Turner 1998). With respect to *loading cycles,* i.e., the number of load repetitions required to activate the adaptive response, very few are required to elicit a maximal response (Umemura et al. 1997). Prolonged loading provides no further benefits (Turner 1998). Instead, as loading duration increases, bone formation tends to saturate (Rubin & Lanyon 1984; Umemura et al. 1997; Turner 1998). Finally, bone formation increases when load cycles are delivered in separate bouts with *rest-recovery periods* in between (Robling, Burr & Turner 2000; Robling, Burr & Turner 2001; Robling et al. 2002).

2.2.2 Mechanoadaptive pathways

The potency of the strain stimulus is determined by complex interplay between the strain characteristics. When the mechanical loading, and hence the strain stimulus, is greater or lower than the customary level, modeling and remodeling are initiated (Hughes et al. 2020). The altered bone shape and structure (through modeling) and tissue-level mechanical properties (through remodeling) determine whole-bone stiffness, which again influences the strain response to mechanical loading (Hughes et al. 2020).

There are four primary mechanoadaptive pathways: formation modeling, targeted remodeling, resorption modeling and disuse-mediated remodeling (Hughes et al. 2020). Formation modeling and targeted remodeling accompany a greater than customary strain stimulus whereas resorption modeling and disuse-mediated remodeling accompany a lower than customary strain stimulus. In cortical bone, these pathways act as follows. *Formation modeling* increases cortical thickness at the bone shafts by depositing new bone on periosteal and/or endocortical surfaces (Hughes et al. 2020). *Targeted remodeling*, in turn, removes and replaces fatigue-damaged bone tissue (i.e., removes microdamage) (Hughes et al. 2020). Targeted remodeling occurs primarily on the intracortical surface and may result in temporarily elevated porosity and decreased tissue mineralization (Hughes et al. 2020). *Disuse-mediated remodeling* is the first response to an unloading period. It increases intracortical porosity, primarily around the endocortical surface (Hughes et al. 2020). *Resorption modeling* involves independent endocortical resorption that expands the marrow cavity and thins the cortices (Hughes et al. 2020).

2.3 Non-invasive bone strength measurement techniques

The direct assessment of bone strength (i.e., point at which bone yields or fails) is always destructive. Bone strength can, however, be estimated by several non-invasive, imaging-based methods that assess bone density and structure at various depths and according to various scales. Bone mineral density (BMD) reflects the material contribution and is a frequently used surrogate of bone strength.

Dual-energy X-ray absorptiometry (DXA) is, by far, the most widely available and commonly used method of measuring bone both in clinical practice and in research. It is a standard method for the clinical diagnosis of osteoporosis, and it is also used in the assessment of fracture risk (Blake & Fogelman 2010). DXA is based on the variable absorption of x-ray beams by the mineralized and soft tissue components of bone. To separate these components, it utilizes two beams of varying energy (Blake & Fogelman 2010). It is most commonly used for clinically important hip and lumbar spine areas. DXA yields a two-dimensional image of a bone's three-dimensional structure in which density values are areal (g/cm^2) rather than true, volumetric (g/cm^3) values. Hence, areal BMD (aBMD) values are strongly affected by bone size, with larger bones having higher aBMD (Carter, Bouxsein & Marcus 1992). Further limitations of DXA are low resolution, inability to discriminate between cortical and trabecular bone, and potential measurement errors caused by the surrounding soft tissues (Yu et al. 2012). The advantages of DXA include good accessibility, high precision and a low dose of radiation.

Quantitative computed tomography (QCT) is predominantly used for research purposes and has several advantages over DXA. As a three-dimensional modality, it allows measurement of volumetric BMD (vBMD, mg/cm^3) and bone macrostructure, and separate assessment of cortical and trabecular bone, principally in the spine and proximal femur. It also provides separate measures of medullary bone, muscle, and fat compartments. QCT relies on multiple x-ray scans at different angles to create a three-dimensional view of the object. It is less prone to surrounding soft tissue errors (Yu et al. 2012). The disadvantages of QCT include relatively high x-ray doses (ionizing radiation), problems of accessibility and costly equipment (Engelke et al. 2008). Moreover, typical scanning artefacts include partial volume effect and beam hardening. Partial volume effect arises when several types of tissues contribute to a single voxel in the image. Partial volume effects increase with larger voxel size (loss of contrast due to insufficient resolution). Beam hardening, on the other hand, refers to selective attenuation of the low-energy photons of the x-ray beam, and hence to "hardening" of the beam. The voxel grey-scale value (i.e., tissue density) may thus be different in different spatial locations even if the material is the same throughout.

Peripheral QCT (pQCT) is a device for peripheral sites such as the upper and lower limbs. Compared to QCT, it is less costly, uses less radiation, and x-rays are applied to less vulnerable, peripheral sites. Typical (p)QCT-derived bone

outcomes include cross-sectional area (CSA, mm^2), vBMD and bone mineral content (BMC, mg/mm, derived from the density and the known volume) of the total bone and of the trabecular and the cortical compartments. In addition, cortical thickness, periosteal and endosteal circumference, CSMI (for anterior-posterior and medial-lateral planes), polar moment of inertia (along the neutral axis) and strength indices combining geometry and density, such as the strength–strain index (SSI) and the compressive bone strength index (BSI), can all be assessed. SSI reflects a bone's resistance to bending and torsion and BSI its resistance to compression (Kontulainen et al. 2008; MacIntyre & Lorbergs 2012). SSI multiplies the section modulus (SM = CSMI/maximum distance between the outer boundary and center of the cross-section) by the quotient of the measured cortical density and the normal physiological cortical density (1200 mg/cm^3) (Kontulainen et al. 2008). BSI is the product of CSA and density squared (Kontulainen et al. 2008).

As the QCT methodology is limited to macrostructure only, special high resolution pQCT (hr-pQCT) devices have been introduced to measure bone microstructure such as cortical porosity and trabecular architecture (Cheung et al. 2013; Engelke et al. 2013). In addition, a computer modeling technique known as finite element analysis can be applied to hr-pQCT or CT images to assess bone biomechanical function (e.g., stiffness) and strength (e.g., failure load) without physically breaking or deforming the bone (Whittier et al. 2020; Kontulainen & Johnston 2021).While first-generation hr-pQCT is restricted to the distal tibia and distal radius only, the recent introduction of second-generation hr-pQCT also allows scanning of the shaft regions (30% of bone length) (Whittier et al. 2020). Despite gaining popularity, it is rather costly, and the techniques are still under development (Hart et al. 2020).

2.4 Age-related bone deterioration

With aging, the cellular machinery responsible for bone modeling and remodeling becomes impaired leading to deterioration in bone composition, structure and function (Boskey & Coleman 2010; Demontiero, Vidal & Duque 2012). Over the life course, bone mass and strength increase during growth, plateau in young adulthood, and begin to decline progressively after about 35 years of age (Frost 1997; Baxter-Jones et al. 2011; Jackowski et al. 2011). The onset and the rate of the bone loss varies according to the skeletal site (Macdonald et al. 2011) and sex. In premenopausal women and in men up to age 50, aBMD declines by approximately 0.5-1% per year (Warming, Hassager & Christiansen 2002; Chodzko-Zajko et al. 2009). Thereafter, bone deterioration accelerates, especially in women during menopause, when bone resorption accelerates due to menopause-related estrogen withdrawal (Suominen 2006; Khosla 2010). Trabecular bone, partly because of its greater surface-to-volume ratio and greater metabolic activity, is lost earlier and, at least initially, at a greater rate than cortical bone (Riggs et al. 2008). Cortical bone loss begins mainly in mid-life in

women and after age 70-75 in men, whereas trabecular bone loss already commences in young adulthood (Riggs et al. 2008).

Modeling-based periosteal bone formation decreases with aging, while the alterations in remodeling include increased activation frequency, i.e., a higher remodeling rate, and a negative balance between the amounts of bone resorbed and formed within individual BMUs (Martin & Seeman 2008; Compston 2011). The negative balance may result from increased resorption, reduced formation, or both, and it may operate individually or in conjunction with the increased remodeling rate (Martin & Seeman 2008; Compston 2011).

Age-induced changes differ in part across the different bone tissue types. In trabecular bone, aging is manifested by trabecular thinning, loss of connectivity and the complete loss of trabecular elements (Seeman & Delmas 2006; Macdonald et al. 2011; Chen et al. 2013). The increased remodeling rate, especially in combination with increased resorption within an individual BMU, is mainly associated with increased trabecular perforation and loss of connectivity (Compston 2011). Decreased formation is predominantly associated with trabecular thinning and better preservation of the trabecular microarchitecture. However, as trabecular thinning progresses, the probability of perforation also increases (Compston 2011). Loss of connectivity, which is the primary mechanism of trabecular bone loss in women, is more deleterious to bone strength than the thinned but well-connected trabeculae typically found in older men (van der Linden et al. 2001; Khosla & Shane 2016).

Typical changes in cortical bone include decreased cortical density and thickness, and increased porosity (Demontiero, Vidal & Duque 2012). The mechanisms behind these changes include a lower rate of periosteal bone formation and changes in the rate and balance of endocortical and intracortical remodeling (Compston 2011). Decreased periosteal bone formation and increased endocortical resorption lead to decreased cortical thickness (Demontiero, Vidal & Duque 2012). Cortical bone at the endocortical surface becomes porous and its architecture begins to resemble that of trabecular bone (trabecularization of cortical bone). Endocortical bone loss is greater in women (Lauretani et al. 2008; Demontiero, Vidal & Duque 2012). In men, greater levels of periosteal bone formation somewhat compensate for the increasing levels of endocortical bone loss (Duan et al. 2003; Demontiero, Vidal & Duque 2012). The rate and balance of intracortical remodeling also changes with aging, resulting in increased cortical porosity (Zebaze et al. 2010). Despite its later onset, cortical bone loss makes a major contribution to increased bone fragility during aging, as the majority of the bone mass is in the cortical compartment (Zebaze et al. 2010).

2.4.1 Factors contributing to bone loss during aging

Several intrinsic and extrinsic factors contribute to age-related bone loss. Intrinsic factors include, for example, genetics, hormonal status and peak bone mass in youth whereas extrinsic factors include physical activity, nutrition, comorbid medical conditions and drugs (Clarke & Khosla 2010; Demontiero, Vidal & Duque 2012; Kirk et al. 2020). Twin studies have indicated that bone properties

are largely genetically determined (Mikkola et al. 2008; Wagner et al. 2013). Peak bone mass, which is attained during growth in childhood and adolescence, is under strong genetic influence (Ralston & Uitterlinden 2010) and is obviously a major determinant of bone mass later in life (Khosla 2013). The heritability of age-related bone loss, however, is less clear (Ralston & de Crombrugghe 2006; Mitchell & Yerges-Armstrong 2011).

Hormonal factors such as estrogens, androgens, growth hormone and parathyroid hormone (PTH) are important for bone accrual, maintenance, and preservation over the life course (Almeida et al. 2017; Laurent et al. 2019). Overall, men have higher aBMD throughout their lives, especially during sexual maturation, when bone size is increased by testosterone (Clarke & Khosla 2010). Estrogen is a major regulator of bone metabolism in both women and men. Estrogen suppresses bone resorption whereas estrogen and testosterone are both important for the maintenance of bone formation (Khosla 2013). The declining levels of both estrogens and androgens during aging and menopause likely contribute to the age-related loss of bone mass and strength in both sexes (Clarke & Khosla 2010; Khosla 2013; Almeida et al. 2017). Age-related decreases in growth hormone may also contribute to decreased bone formation (Clarke & Khosla 2010).

Of the nutritional factors, dietary protein, vitamin D and calcium, intake of which are inadequate in many elderly individuals (Jyväkorpi et al. 2015), play a particularly important role in bone metabolism (De Rui et al. 2019). Calcium and protein are the major building blocks of bone tissue, whereas vitamin D has an important role in enhancing calcium absorption from the diet, which again is crucial for normal mineralization of the skeleton, and for maintenance of systemic calcium homeostasis (Feldman, Krishnan & Swami 2013). Decreased calcium absorption stimulates an increase in PTH secretion, which again increases bone resorption and calcium efflux from bone into the blood (Demontiero, Vidal & Duque 2012; Nissenson 2013). Several other factors, such as long-term estrogen deficiency may also contribute to increasing PTH levels during aging (Clarke & Khosla 2010; Demontiero, Vidal & Duque 2012).

Several medical conditions and certain drugs, such as corticosteroids, may cause bone loss and/or impairment of bone strength through alterations in remodeling (Weng & Lane 2007). In addition, medical conditions (and associated catabolic states) may affect bone through impaired physical performance (reduced bone loading) and/or through diminished musculoskeletal responses to exercise. Among the anti-osteoporotic drugs, bisphosphonates are the most commonly prescribed. Bisphosphonates increase bone strength by suppressing bone resorption activity (Drake, Clarke & Khosla 2008). However, the long-term use of bisphosphonates may cause potentially serious side effects (Woo, Hellstein & Kalmar 2006). Furthermore, long-term inhibition of bone resorption may suppress bone remodeling and possibly limit bone cell response to exercise.

Several behavioral factors, such as long-term smoking habits continued into older age and reduced physical activity/exercise may also contribute to bone loss via multiple direct and indirect pathways. Smoking affects bone health directly

by inducing changes in bone turnover and indirectly, for example, through altering calcium metabolism and hormonal function (Al-Bashaireh et al. 2018). Physical exercise has a major influence on peak bone mass accumulation during growth (Wang et al. 2007). With respect to its role in age-related bone loss, it is uncertain whether bone loss later in adult life is an adaptation to reduced mechanical loading in less active elderly individuals or occurs due to alterations in bone mechanosensation or mechanoresponsiveness (Javaheri & Pitsillides 2019). It may be that in the aged skeleton, the ability to form new bone declines, or the stimulus for bone formation is absent or no longer effective in activating the bone cells (Javaheri & Pitsillides 2019). Although not fully known, current evidence suggests that while mechanoresponsiveness remains largely unaltered (Klein-Nulend et al. 2002; Leppänen et al. 2008), some decrease in mechanosensitivity may occur (Hemmatian et al. 2017).

Finally, muscle mass and strength have a potential role in preserving bone during aging. Muscle and bone are tightly interconnected tissues both anatomically and functionally. Muscle contraction provides the greatest loads on bones, exceeding the gravitational forces associated with weight (Burr 1997; DiGirolamo, Kiel & Esser 2013). In weight-bearing impact activities, muscles may place additional forces on bones or, at the same time, protect them from overuse injuries (e.g., stress fractures) by transmitting and attenuating loads resulting from impacts (Avin et al. 2015). Metabolically, the positive relationship between bone and muscle can be traced to several muscle-secreted (myokines) and bone-secreted (osteokines) endocrine and paracrine factors that affect other nearby and distant tissues and organs (DiGirolamo, Kiel & Esser 2013; Cianferotti & Brandi 2014; Hart et al. 2017; Kirk et al. 2020). The effect of myokines on bones and the effect of osteokines on muscles may occur both directly and indirectly through the actions of other tissues (Kirk et al. 2020). In addition, muscles and bones share genetic influences and pathways (DiGirolamo, Kiel & Esser 2013; Hart et al. 2017). Overall, muscle and bone interact to maintain their structure and function, and their adaptation to increased or decreased loading is interrelated (Kirk et al. 2020). Age-related loss of bone and muscle proceed in parallel, and the loss of muscle mass and strength may also contribute to age-related bone loss (Laurent et al. 2019; Kirk et al. 2020). The changes in muscle, both anabolic and catabolic, precede the changes in bone, which occur at a much slower rate (Hart et al. 2017; Ireland & Rittweger 2017). In addition to temporal association, alterations in muscle size, density and strength are positively correlated with the corresponding parameters in bone, further highlighting the contribution of muscles in preserving bone (Hart et al. 2017).

2.4.2 Osteoporosis

Age-related bone loss predisposes the skeleton to the onset of osteoporosis. Osteoporosis is a disease characterized by diminished bone strength, enhanced bone fragility and increased fracture risk. Typical sites for osteoporotic fractures are the spine, wrist, humerus and hip. Osteoporosis may develop through excessive bone loss and/or through abnormalities in bone acquisition during

growth. Skeletal integrity may be diminished by multiple genetic, physical, hormonal, and nutritional factors acting alone or in concert (Marcus, Dempster & Bouxsein 2013). Risk factors for osteoporosis include factors such as age over 50, female sex, family history of osteoporosis, nutritional deficiencies, and low physical activity. The WHO criterion for osteoporosis is an aBMD value of 2.5 standard deviations below that of healthy young women (T-score), typically measured by DXA (Kanis et al. 1994). A T-score between -1 and -2.5 indicates osteopenia.

2.4.3 Hip fractures and post-hip fracture bone loss

Hip fracture is the most serious consequence of osteoporosis, although not all hip fractures are linked with osteoporosis. Key determinants of hip fractures include osteoporosis, falls, and older age, which is a risk factor for both osteoporosis and falls (Benetos et al. 2007). Over 90% of hip fractures occur following a fall (Parkkari et al. 1999); in older people, a hip fracture typically results from a low-energy fall from standing height. There are two main types of hip fractures: intracapsular (femoral head and neck) and extracapsular (trochanteric) fractures. Most hip fractures require surgical treatment. Fracture location and severity mainly define the type of surgery used. Treatments include internal fixation using screws, and total or partial replacement (arthroplasty or hemiarthroplasty).

Hip fractures are a major public health problem; both short-term and long-term outcomes for patients are usually poor. Hip fractures in older adults are associated with high rates of morbidity, disability, loss of independence, long-term institutionalization, reduced quality of life, and premature death (Nihtilä et al. 2008; Kim et al. 2012; Neuman et al. 2014; Salpakoski et al. 2014; Edgren et al. 2015; Dyer et al. 2016; Peeters et al. 2016; Katsoulis et al. 2017). Approximately half of hip fracture survivors do not regain their pre-fracture health status or level of mobility (Dyer et al. 2016; Peeters et al. 2016), and best practices supporting recovery continue to be lacking (Handoll, Sherrington & Mak 2011).

Hip fracture is followed by a substantial and long-term decline in bone properties (Magaziner et al. 2006; Mikkola et al. 2007; Reider et al. 2010; Rathbun et al. 2016a; Rathbun et al. 2016b). In the contralateral hip, as measured by DXA, the loss of bone density, structure, and strength over the year after fracture far exceeds the decrements from normal aging, in both men and women (Magaziner et al. 2006; Reider et al. 2010; Rathbun et al. 2016a; Rathbun et al. 2016b). For example, it has been estimated that aBMD at the femoral neck declines by approximately 5% during the first post-fracture year (Wehren et al. 2004; Magaziner et al. 2006). This decline was found to be 12 times greater than in a non-fracture cohort (Magaziner et al. 2006). The larger part of the decline in aBMD probably occurs during the first two months post fracture (Fox et al. 2000; Magaziner et al. 2006), whereas the greatest decrements in hip geometry have been reported to occur during the first six months (Reider et al. 2010). Moreover, Wehren et al. (2004) found that bone loss in women with high aBMD at baseline was greatest within the first two months post fracture, whereas bone loss in women with low aBMD was greatest between six and 12 months post fracture.

However, no between-group differences were observed in cumulative loss over the year. In addition, cross-sectional studies using pQCT have revealed marked impairments in tibial properties in both the nonfractured and fractured leg (Mikkola et al. 2007; Vico et al. 2008). These reductions were most evident in bone structure (Mikkola et al. 2007; Vico et al. 2008) and correlated with hip aBMD measured by DXA (Vico et al. 2008). Significant side-to-side differences favoring the non-fractured leg were observed as long as approximately 3.5 years post fracture (Mikkola et al. 2007). No longitudinal studies, however, exist on post-hip fracture bone weakening, either using 3D imaging or examining both the fractured and the non-fractured leg.

Despite the extensive research on the factors contributing to overall bone loss, systematic exploration of the factors contributing to post-hip fracture bone deterioration has been rather scarce (Wehren et al. 2004; Wehren et al. 2005). Catabolic reactions caused by the fracture and its surgical treatment promote significant bone loss (Hedström, Ljungqvist & Cederholm 2006). In addition, a notable part of post-hip fracture bone loss can be assumed to be caused by disuse, especially in the affected leg (Mikkola et al. 2007). Immobilization studies have demonstrated that weight-bearing is essential for bone maintenance, and disuse-related bone loss can be recovered following re-ambulation (Rittweger & Felsenberg 2009). Wehren et al. (2004; 2005) examined multiple demographic, health, lifestyle, clinical, surgical, and functional characteristics at baseline, but found no associations of these with aBMD one year later. These studies did not, however, examine measured changes in bone characteristics.

In addition to bone deterioration, muscle mass, strength, and physical function also decline significantly following a hip fracture (Fox et al. 2000; Fredman et al. 2005; Wehren et al. 2005). Together, these decrements increase the risk for a subsequent hip fracture and other osteoporotic fractures. A low level of physical function is a risk factor for poorer overall recovery after hip fracture. Patients with difficulty in post-discharge ability to walk outdoors showed poorer recovery of physical function during the post-fracture year (Sipilä et al. 2016). Low physical function could also be related to bone loss through a decrease in the amount of bone-loading physical activity and/or in the ability to load bones effectively. Moreover, lower muscle mass, measured as lean body mass (LBM), has also been associated with poorer functional recovery after hip fracture (Di Monaco et al. 2007; Di Monaco, Castiglioni & Di Carlo 2018). The strong interactions that exist between muscle and bone may mean that muscle mass also contributes to accelerated bone loss, including following a hip fracture.

2.5 Effects of exercise on bone during adulthood and aging

Physical exercise has beneficial effects on bone at all ages. Based on animal studies on mechanical loading characteristics (strain environment), human studies have concluded that bone responds best to exercise that includes high-magnitude loads that are dynamic, rapid, multidirectional, have relatively few

repetitions, and are applied at intervals (Heinonen et al. 1995; Heinonen et al. 1996; Lanyon 1996; Nikander et al. 2005; Kistler-Fischbacher, Weeks & Beck 2021a). Examples of such are high-intensity strength training and weight-bearing high/odd-impact-loading activities such as plyometrics, gymnastics and sprinting. Progressive strength training is a powerful stimulus for improving not only muscle strength, but also bone strength as it places a diverse range of forces on bone via the direct effect of muscle pull and by increasing the effect of the gravitational forces acting on bone (Daly et al. 2019). High-velocity power training, on the other hand, has potential for inducing rapid strain rates on bone and also for improving functional outcomes important in falls prevention. Moreover, different training modes may have differing site-specific effects on bones. In the lower leg, high-impact training appears to have superior effects on the distal sites whereas high-intensity resistance training has greater effects on the shaft region (Lambert et al. 2020). Low-impact aerobic training, such as walking or jogging, appears to have little or no effect on improving or maintaining bone (Taaffe et al. 2013; Daly et al. 2019). Similarly, non-weight-bearing activities involving forceful muscular contractions, such as swimming and cycling, appear to be less beneficial for the skeleton (Nikander et al. 2005; Nikander et al. 2006; Rector et al. 2008; Taaffe et al. 2013).

In addition to loading mode, the American College of Sports Medicine (ACSM) has listed five principles pertaining to exercise programs designed to optimize musculoskeletal health: 1) specificity, 2) overload, 3) reversibility, 4) initial values, and 5) diminished returns (Kohrt et al. 2004). *Specificity* refers to the site-specific (instead of systemic) nature of bone adaptations to mechanical loading. Therefore, exercise should load the target bones. In the prevention of osteoporosis, preferred bone sites include the hip, spine and wrist, as these are the most common sites of osteoporotic fractures. *Overload* means that the exercise must be progressive and exceed customary loads, whereas according to the principle of *reversibility,* positive osteogenic effects are not maintained if the loading stimulus is removed. Furthermore, the greatest skeletal responses occur in those with the lowest *initial values*, and after initial adaptation, further exercise-induced effects are likely to be small and slow (*diminished returns*). However, the initial values in skeletal adaptation may, in part, reflect the fact that, assuming similar absolute load, smaller and weaker bones experience greater strain than larger and stronger bones (Daly et al. 2019). Diminished returns relates not only to initial values but also to overload in that after initial adaptation, unless loading is progressive, less strain is experienced (Daly et al. 2019).

Exercise-induced gains in bone mass, structure and strength appear to be greatest during childhood and adolescence, whereas during adulthood, the gains are typically modest or sometimes even absent (Taaffe et al. 2013; Ireland & Rittweger 2017). In adults, exercise likely maintains bone or reduces bone loss rather than increases bone strength (Taaffe et al. 2013), and it has been suggested that the focus of exercise should gradually shift to falls prevention rather than increasing bone strength (Kontulainen & Johnston 2021). Meta-analyses and systematic reviews (Martyn-St James & Carroll 2009; Gómez-Cabello et al. 2012;

Marques, Mota & Carvalho 2012; Taaffe et al. 2013; Zhao, Zhao & Xu 2015; Zhao, Zhang & Zhang 2017; Benedetti et al. 2018; Kistler-Fischbacher, Weeks & Beck 2021a; Kistler-Fischbacher, Weeks & Beck 2021b) have reported that the most effective physical activity programs for preserving or increasing bone health in older populations include moderate to high-intensity, progressive resistance and power training, short bouts of diverse weight-bearing impact loading activities, and challenging balance and mobility training. Multicomponent exercise programs or training combining strength and impact training seem to be especially effective (Zhao, Zhao & Xu 2015; Zhao, Zhang & Zhang 2017; Pinheiro et al. 2020) as they simultaneously improve several musculoskeletal and functional outcomes (Park et al. 2008).

There is considerable evidence for a positive, although modest, effect of exercise on aBMD in the femoral neck and spine in postmenopausal women (Howe et al. 2011; Kelley, Kelley & Kohrt 2012; Sañudo et al. 2017; Zhao, Zhang & Zhang 2017; Shojaa et al. 2020; Kistler-Fischbacher, Weeks & Beck 2021a; Kistler-Fischbacher, Weeks & Beck 2021b), whereas in middle-aged and older men, the evidence is limited and more research is needed (Bolam, van Uffelen & Taaffe 2013; Kemmler et al. 2018; Kemmler et al. 2020). Owing to the sexual dimorphism in the musculoskeletal system that emerges during adolescence and aging (Laurent et al. 2014), the osteogenic response to exercise during aging may be sex-dependent, and thus studies are needed on both sexes. Men may respond better owing to hormonal differences and possibly greater loading stimuli due to their larger body and muscle size (Guadalupe-Grau et al. 2009; Kontulainen & Johnston 2021). The experimental evidence for sexual dimorphism in the osteogenic response to exercise is, however, rather weak (Guadalupe-Grau et al. 2009). It has been suggested, although not by all (Järvinen, Kannus & Sievänen 2003), that the reduced response that may occur in women probably relates to menopause-related estrogen deficits that could decrease bone mechanosensitivity (Klein-Nulend et al. 2015). Moreover, owing to greater age-related bone deterioration, the effect of exercise in older women is probably limited to reducing the rate of bone deterioration whereas in older men, increases in bone strength may be more in evidence.

Another important unanswered question is whether exercise delivered to older adults has positive effects on bone cross-sectional geometry and strength that are not captured by DXA. The current experimental evidence on geometrical adaptation in older people is scarce and somewhat conflicting (Hamilton, Swan & Jamal 2010; Nikander et al. 2010; Polidoulis, Beyene & Cheung 2012). Some meta-analyses and systematic reviews have found positive, but modest effects on cortical and trabecular vBMD (Polidoulis, Beyene & Cheung 2012) and on cortical bone mass and geometry (Hamilton, Swan & Jamal 2010) whereas others have found no effects on geometry and strength (Nikander et al. 2010). Since then, RCTs on middle-aged and older people have found positive effects on proximal femoral bone mass after impact training (Allison et al. 2015) but no effects on mid-femoral or mid-tibial vBMD, geometry or strength after strength training or combined strength and impact training (Kukuljan et al. 2011; Ashe et al. 2013).

The mixed results and the lack of positive effects on bone geometry and strength may be attributed to the short duration and inadequate power of the trials, variability in training programs and study populations, and lack of intensity, specificity, or progression of the training programs. In addition, the overall osteogenic potential of exercise appears to be diminished in older people; this may be explained by several potential factors such as the reduced mechanosensitivity (and/or mechanoresponsiveness) of older bone, and a reduction in the rate and extent of the bone modeling required for large gains in bone geometry. The thresholds of strain sufficient to elicit osteogenic adaptation appear to be higher in older bone (Guadalupe-Grau et al. 2009; Meakin et al. 2014; Cauley & Giangregorio 2020) and require a sufficiently large mechanical stimulus. Reduced physical functioning may, however, limit the ability, tolerance, or willingness of older people to participate in exercise at the intensity required to stimulate osteogenic adaptation. Reduced muscle mass and function may also affect through muscle-bone interactions. Owing to age-related bone loss and the reversibility of exercise-induced bone gains, loading should be continuous and progressive in order to prevent bone deterioration.

2.5.1 Long-term high-intensity training and bone during adulthood and aging

Observational athlete studies have suggested that combined sprint, strength and plyometric training provide a powerful osteogenic training stimulus for the lower body skeleton during adulthood and aging (Suominen & Rahkila 1991; Suominen 1993; Welch & Rosen 2005; Wilks et al. 2009a; Wilks et al. 2009b; Wilks, Gilliver & Rittweger 2009; Nowak et al. 2010; Korhonen et al. 2012; Gast et al. 2013; Rantalainen et al. 2014; Piasecki et al. 2018). Studies on middle-aged and older sprint athletes have shown them to have superior bone strength when compared to non-active counterparts (Wilks et al. 2009a; Rantalainen et al. 2014), or even to a younger physically active reference group (Korhonen et al. 2012). Cross-sectional findings indicate that in adult bone shafts, mechanical loading appears to improve bone strength through changes in the cross-sectional geometry (cortical area and cortical thickness) (Suominen 2006; Wilks et al. 2009a; Rantalainen et al. 2010; Korhonen et al. 2012) and redistribution of bone mass (Ma et al. 2009; Bailey, Kukuljan & Daly 2010; Rantalainen et al. 2010; Korhonen et al. 2012) rather than through changes in vBMD (Rantalainen et al. 2010; Korhonen et al. 2012). Mass distribution analyses of mid-shaft sites have revealed increased bone mass mainly in the anterior-posterior direction, as manifested by improved direction-specific bending strength at the maximum axis (I_{max}) (Ma et al. 2009; Bailey, Kukuljan & Daly 2010; Rantalainen et al. 2010; Korhonen et al. 2012). The improved I_{max} probably relates to posterior bending, which is the habitual loading pattern during sprint training and other weight-bearing activities (Yang et al. 2014). In the distal parts of the bone, physical activity seems to be associated with increased trabecular bone mass, vBMD, and compressive strength (Ma et al. 2009; Wilks et al. 2009a).

The experimental evidence on the osteogenic effects of high-intensity exercise among older athletes is, however, lacking. Moreover, the long-term effects of intensive training remain unclear, and it is not known whether age-related bone deterioration can be decreased or prevented via regular intensive exercise. Cross-sectional studies have shown age-related bone loss in regularly training male and female masters sprinters (Wilks et al. 2009b; Korhonen et al. 2012). These studies may not, however, have revealed the true longitudinal effects of aging and training on bone (Lauretani et al. 2008). Longitudinal changes derived from cross-sectional settings could, for example, reflect cohort differences rather than actual changes over time. A recent longitudinal study by Ng et al. (2020) found that community-dwelling older men who engaged in high and rapid impact physical activity maintained higher aBMD at the hip and spine over five years. Similar results have been observed in middle-aged and older male and female masters long distance runners (Wiswell et al. 2002; Hawkins et al. 2003). These studies have not, however, examined changes in bone geometry, strength, or volumetric density. Longitudinal investigations on bone traits in masters sprint/power athletes are also scarce. In their 4-year follow-up, Ireland et al. (2020) found greater maintenance of mid-tibial and distal tibia properties in middle-aged and older male and female power athletes compared to endurance athletes. To date, however, no studies exists on the importance of sustained sport-specific training on bone aging.

2.5.2 Exercise and post-hip fracture bone loss

Current exercise recommendations for individuals with reduced bone strength, and hence increased fracture risk, include avoidance of high-impact loading and exercises requiring explosive and abrupt movements (Giangregorio et al. 2014). For high-risk individuals, reduced impact loading activities such as heel drops, stair climbing and other weight-bearing exercises are preferred (Taaffe et al. 2013, Cauley & Giangregorio 2020). As with average aging populations, multicomponent programs that emphasize progressive strength training targeting major muscle groups and balance training to prevent falls and falls-related fractures are also recommended for high-risk individuals (Taaffe et al. 2013).

To date, only a few studies have examined the osteogenic effects of exercise in older people with low bone mass and reduced physical functioning. Even fewer studies have targeted accelerated post-hip fractural bone loss (Binder et al. 2004; Orwig et al. 2011), and no studies utilizing 3D bone imaging have been conducted in patients with hip fracture or comparable subjects. A yearlong home-based intervention combining aerobic stepping exercise with balance training and resistance exercises (applying resistance bands and ankle and wrist cuff weights) (Orwig et al. 2011) was unable to prevent post-hip fractural bone loss in the contralateral hip of older women with hip fracture. Similarly, a more intensive 6-month outpatient rehabilitation program including progressive resistance training (Binder et al. 2004) had no additional effect on the total or regional BMD of the men and women with hip fracture compared to a low-

intensity home exercise program. In that study, it is notable that no significant bone loss was observed in either of the groups during the 6-month trial. However, both groups also received calcium and vitamin D supplements, and hence the possible effects of training and nutrition cannot be separated.

The few studies on frail older people comparable to people with hip fracture have also shown minor or no effects of exercise on bone density. A 6-month home-based exercise program including strength training and aerobic training had no effects on femoral neck or lumbar spine aBMD in osteoporotic postmenopausal women with a vertebral fracture (Papaioannou et al. 2003). Similarly, the 9-month moderate-to-high-intensity multi-component exercise program by Villareal et al. (2004) did not increase aBMD in comparison to low intensity home exercise in frail older men and women receiving supplementary calcium and vitamin D. In both studies, aBMD remained unchanged over the follow-up period in both the intervention and control groups (Papaioannou et al. 2003; Villareal et al. 2004). In their 30-month impact training trial on older women with low aBMD, Korpelainen et al. (2006) found a positive effect on BMC at the trochanter, but no effect on aBMD at the hip. A systematic review on the effects of exercise in older people with osteopenia/osteoporosis suggested positive effects on bone density after at least 12 months of weight-bearing aerobic training with or without muscle-strengthening exercises (de Kam et al. 2009). However, the exercise interventions included in the review varied considerably.

Recently, the current exercise recommendations for older people at high risk have been challenged by studies that have found supervised high-intensity strength and/or impact training safe, feasible and effective for older men (Harding et al. 2020; Kemmler et al. 2020) and women (Watson et al. 2015; Watson et al. 2017) with low bone mass, and for post-menopausal women with mild osteoarthritis (Multanen et al. 2014; Multanen et al. 2017). Favorable effects have been observed on lumbar spine and proximal femur BMD (Watson et al. 2015; Kemmler et al. 2020), femoral neck BMC (Multanen et al. 2014) and geometry (Multanen et al. 2017; Watson et al. 2017; Harding et al. 2020), and bone strength at the distal tibia and radius (Harding et al. 2020). Similarly, a small-scale trial on postmenopausal women with osteopenia (Bolton et al. 2012) reported modest improvements in total hip BMD after 12 months of combined high-impact, strength, and balance exercises. Despite being osteopenic/osteoporotic (or having osteoarthritis), the participants in these studies were relatively well-functioning and not comparable to people with hip fracture. Thus, it is not currently known whether older people with low physical functioning as well as weak bones are able to participate in physical activities that have beneficial effects on their bones. It is also not known whether extremely fragile bones with clinical manifestation of osteoporosis, such as those in patients with hip fracture, are able to adapt to increased loading. Moreover, most trials have focused on older adults considerably younger in age than people with hip fracture on average, while a knowledge also gap exists on the osteogenic effects of exercise among the very elderly. Exercise appears to be highly effective against disuse-related bone loss, at least against complete lack of loading (Ireland & Rittweger

2017). Hence, exercise might also be effective against post-hip fractural bone loss. There is some evidence that even low-intensity resistance training may be effective in counteracting age-related bone loss in those with reduced bone mass (Souza et al. 2020), although more research is needed to confirm this. An alternative training form, high frequency whole body vibration training (WBV), has also been proposed as a promising training modality for bone health, especially for those unable/unwilling to participate in traditional exercise. However, the results on the effects of WBV are mixed (Jepsen et al. 2017; Mohammad Rahimi et al. 2020) and there have been safety concerns (such as pain and falls risk) related to high-intensity platforms (Wysocki et al. 2011).

3 PURPOSE OF THE STUDY

The purpose of this doctoral dissertation was to investigate the effects of physical exercise on bone adaptations in high-performance masters athletes with a life-long training history, and in older adults who have sustained a recent hip fracture. In addition, follow-up studies were conducted to investigate the longitudinal associations of physical exercise and physical function with bone changes among the athletes and the patients with hip fracture. By examining these groups situated at the opposite ends of the physical activity and bone health spectrum, this research aimed at enhancing our understanding of the role of physical exercise and physical function in bone adaptation and maintenance during aging. The specific aims of this PhD thesis were:

1. To investigate the effects of a 20-week high-intensity strength and sprint training program on tibial bone structure and strength in middle-aged and older masters athletes. (Study I)
2. To examine the role of continued strength and sprint training on 10-year longitudinal changes in tibial bone structure, density, and strength in the masters athletes. (Study II)
3. To investigate the effects of a 12-month home-based physical rehabilitation program on tibial bone density, structure and strength in older adults recovering from a recent hip fracture. (Study III)
4. To examine physical function and lean body mass as predictors of post-hip fracture bone deterioration. (Study IV)

4 MATERIALS AND METHODS

4.1 Study designs and participants

This dissertation utilizes data from two different datasets collected for two different research projects conducted in the Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä: the Athlete Aging Study (Athlas) and the Promoting Mobility after Hip Fracture (ProMo) study. The datasets, designs and participants are summarized in Table 1.

TABLE 1 Datasets, designs, and participants in the different studies.

Study	Dataset	Design	N	Participants
I	Athlas	20-week randomized controlled trial	72	40- to 85-year-old male sprint athletes
II	Athlas	10-year follow-up	69	40- to 85-year-old male sprint athletes
III	ProMo	12-month randomized controlled trial	81	Community-dwelling men (22%) and women (78%) aged 60 and over recovering from a hip fracture
IV	ProMo	12-month prospective follow-up	81	Community-dwelling men (22%) and women (78%) aged 60 and over recovering from a hip fracture

4.1.1 Athlete Aging Study (Studies I & II)

The Athlete Aging Study (Athlas) was a larger research project investigating the effects of age and long-term sprint training on musculoskeletal characteristics and neuromuscular function among male masters athletes (Korhonen et al. 2006; Korhonen et al. 2012). The study included a 20-week RCT (ISRCTN17271498) and a 10-year follow-up. The study flow is shown in Figure 2. In the first study phase, a total of 111 athletes with a successful competition history in international or national masters sprinting events were contacted by a personal letter. Potential participants' addresses were obtained from track and field organizations. The letter included a questionnaire on the athletes' training history, current training, competition performance, and sports injuries or diseases limiting physical training. Based on the questionnaire responses (n=106), eighty-three eligible and voluntary athletes from all over Finland were invited to participate in the baseline measurements. Inclusion criteria included ongoing systematic training and competing, and age ≥40. The exclusion criteria were medications affecting bone metabolism and uncontrolled medical conditions or musculoskeletal disorders which would contraindicate exercise or limit training program participation.

After the baseline measurements, the athletes were randomly assigned into an experimental (n=40) and a control (n=32) group by drawing lots, separately for each 10-year age group (Study I). In each age group, a higher number of participants was assigned to the experimental than to the control group in order to compensate for the possibility of a higher drop-out rate and larger variance in the results. Follow-up measurements were carried out after the 20-week training period. All the bone outcome assessors were blinded to the treatment allocation.

In the second study phase ten years later, the athletes were contacted by telephone and invited to participate in the follow-up study (Study II). Sixty-nine (83%) of the original 83 participants attended the measurements. Of the remaining participants, five declined to participate due to poor health (n=4) or lack of interest (n=1), three could not be located, and six had died. Follow-up measurements were arranged at the same time of the year (November-December) as at baseline. However, 13 participants were unable to attend this study visit. Their pQCT data were taken from a bone examination carried out during the World Masters Indoor Championships in April of the same year in Jyväskylä. The athletes were allocated to well-trained (n=36) and less-trained (n=33) groups based on self-reports of training and competing status at follow-up. The group of well-trained athletes comprised those who reported ongoing systematic training (sprint training including strength training at least 2 times per week during the preceding year, separated into outdoor and indoor seasons) and competing in masters sprint events. The less-trained group comprised those who reported strength and sprint training less than 2 times per week, did no strength training, had retired from sport activities, had switched to endurance type of training and competing, or reported long-term training breaks during the final years of the 10-year follow-up period. Based on Study I, special emphasis was

put on the maintenance of intensive strength training. The original randomization group (Study I) was not taken into account in the group allocation in Study II.

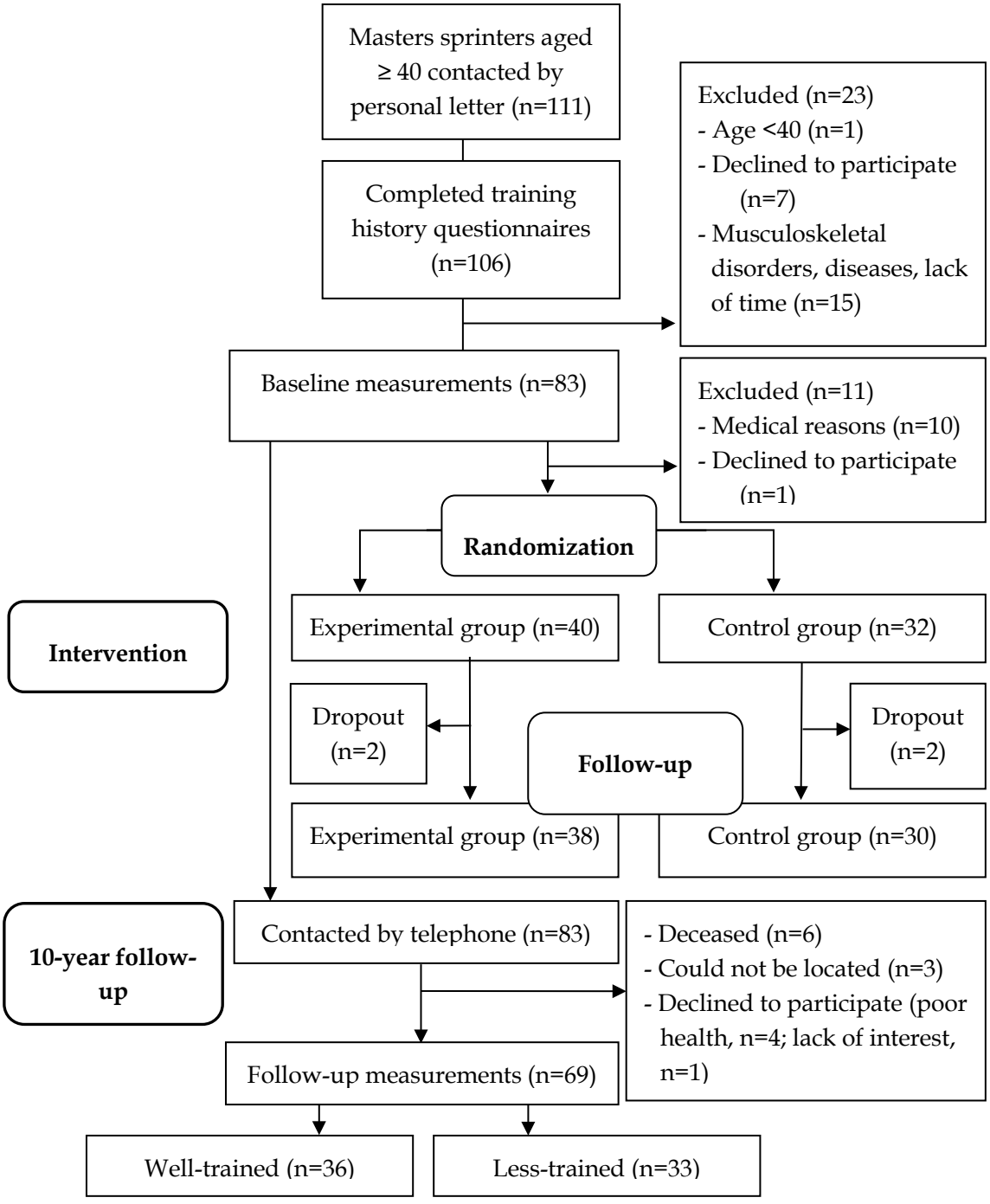

FIGURE 2 Flowchart of the Athlete Aging Study.

Power analysis for the RCT (Study I) was conducted using a sequential method of sample size calculation that allows for more than one primary outcome (O'Brien 1984; Dubey 1985). The analysis was performed by setting α at 0.05 and β at 0.20. The calculations showed that sample sizes varying between 25 and 38

for the experimental and control groups were needed to detect the expected differences in the primary outcomes (mid-tibia CSA_{TOT}, CSA_{CO}, Th_{CO}, I_{maxA}, I_{minA} and I_{polarA}) with the allocated significance level of 0.03. Mid-tibia CSA_{TOT} and I_{polarA} are not reported in this thesis.

4.1.2 Promoting Mobility after Hip Fracture (Studies III & IV)

Promoting Mobility after Hip Fracture (ProMo) was an RCT (ISRCTN53680197) aimed at investigating the effects of a yearlong home-based rehabilitation program on mobility recovery among community-dwelling older adults with a recent hip fracture (Sipilä et al. 2011; Salpakoski et al. 2014). The study flow is shown in Figure 3. Based on patient records at the Central Finland Central Hospital (Jyväskylä, Finland), a total of 269 men and women fulfilled the inclusion criteria [age >60, ambulatory, community-dwelling, operated for a femoral neck or pertrochanteric fracture (ICD-10 code S72.0 or S72.1), resident in the catchment area] and were informed about the study. Of these, 161 were interested and were further visited by a researcher during their inpatient stay at the health care center. After preliminary assessment of eligibility, 136 persons were invited to the baseline measurements, of whom 81 participated in the study. The exclusion criteria included moderate to severe memory problems (Mini Mental State Examination score <18), severe depression (Beck Depression Inventory score >29), a severe cardiovascular or pulmonary condition or some other severe progressive disease, and alcoholism.

The baseline measurements were conducted on average 10 weeks post fracture. Thereafter, the participants were randomly assigned to a rehabilitation (n=40) or a standard care control (n=41) group using a computer-generated randomization sequence generated by a statistician not involved in either the recruitment or data collection processes. The randomization was performed in blocks of 10, which were stratified by gender and surgical procedure (internal fixation versus arthroplasty).

Follow-up measurements were carried out at 3, 6, and 12 months after baseline. For Study IV, data from the rehabilitation and control groups were pooled, and only baseline and 12-month follow-up bone data were utilized. All bone outcome assessors were blinded to participants' group allocation.

An a priori sample size calculation based on previously published longitudinal data on mobility recovery after a hip fracture (Visser et al. 2000). A minimum of 44 participants were needed to be included in both groups to detect the expected difference in mobility recovery at α=0.05 and β=0.20 (Sipilä et al. 2011; Salpakoski et al. 2014).

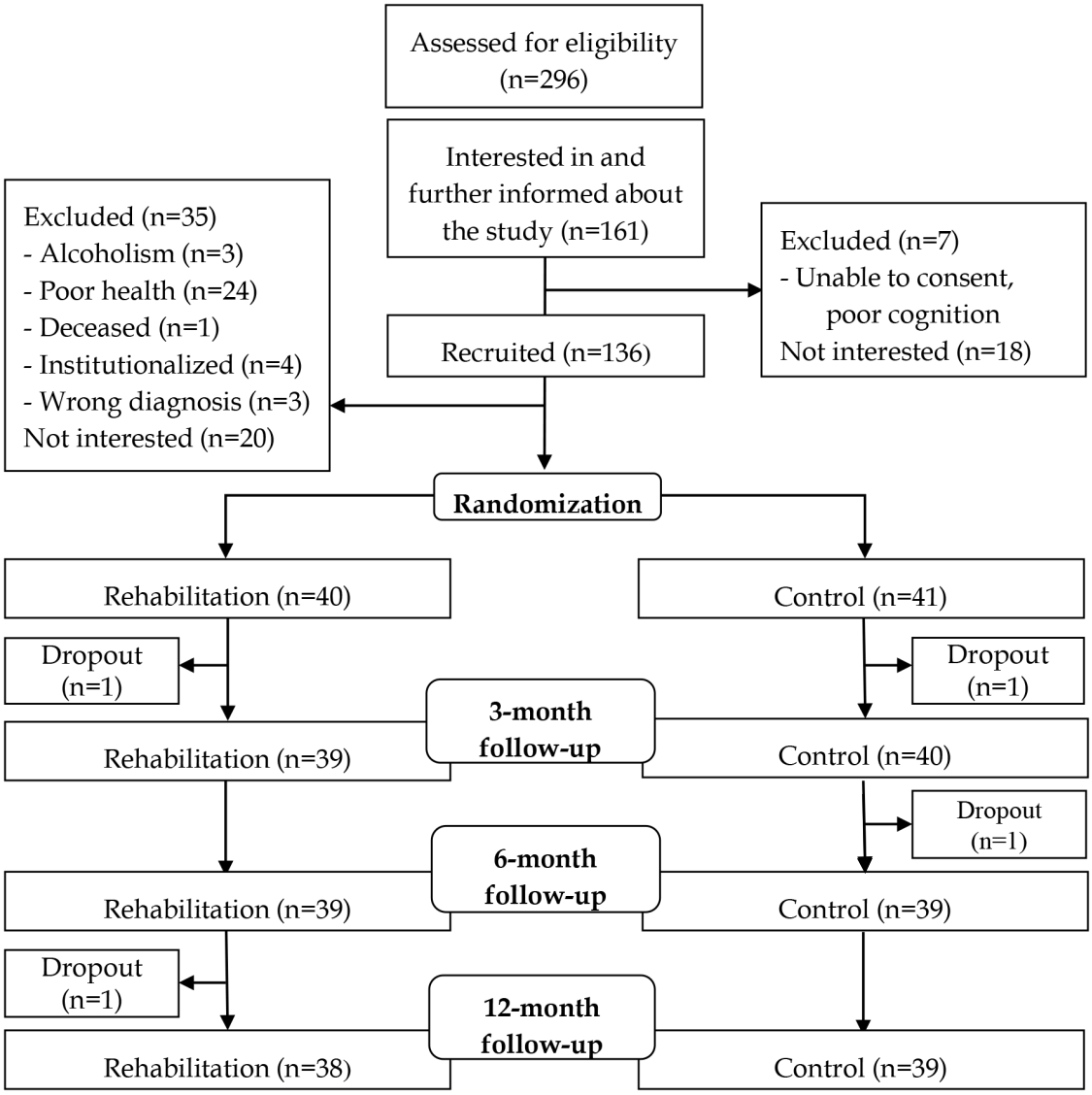

FIGURE 3 Flowchart of the Promoting Mobility after Hip Fracture -study.

4.2 Ethics

The Ethics Committee of the Central Finland Health Care District approved both studies (Athlas and ProMo). In addition, Athlas was also approved by the University of Jyväskylä Ethical Committee. Both studies conformed with the principles of the Declaration of Helsinki. A written informed consent was obtained from all subjects prior to participation. The subjects had the right to withdraw at any time without providing a reason.

4.3 Measurements

The measurements used in this study are summarized in Table 2 and only briefly described in this section. A more detailed description of the methods used is given in the original papers.

TABLE 2 Summary of the measurement methods and variables used in the study.

Measurement	Study	Methods and reference
Bone density, structure, and strength	I-IV	pQCT (XCT-2000, Stratec Medizintechnik, Pforzheim, Germany). Scan analysis software: Geanie 2.1, Commit Ltd., Espoo, Finland (Studies I & II) and OBS cortical bone detection 2.1 (Cervinka, Hyttinen & Sievänen 2012; Cervinka et al. 2015) (Studies III & IV)
Health status		
Presence of chronic conditions	I-IV	Medical examination (Studies I-IV) and medical records (Studies III & IV)
Sports injuries	I, II	Questionnaire, interview
Use of prescription medication	I-IV	Medical examination (Studies I-IV) and medical records (Studies III & IV)
Fracture date and status	III, IV	Medical records
Date and type of surgery	III, IV	Medical records
Smoking history	II-IV	Questionnaire
Anthropometry		
Body height	I-IV	Stadiometer
Body weight	I-IV	Balance beam scale (I & II), Digital scale (III, IV)
Lean body mass,	I, II, IV	Bioimpedance: Spectrum II, RJL Systems, Detroit, MI, USA (Studies I & II) and BC-
Fat %	III	418, TANITA, Tokyo, Japan (Studies III & IV)
Physical activity	III	Questionnaire, modified Grimby scale (Grimby 1986)
Training and competing history and status	I, II	Questionnaire
Compliance with allocated exercise program	I, III	Exercise diary
Physical function/performance		
Rollator use	III, IV	Questionnaire
Difficulty in walking outdoors	IV	Questionnaire
Lower extremity performance	III, IV	Short Physical Performance Battery (SPPB) (Guralnik et al. 1994)
60-m sprint time	I, II	Photocells
Maximal knee extension force	III	Dynamometer chair (Good Strength; Metitur Ltd, Palokka, Finland) (Sipilä et al. 1996)
Leg extension power	III	Nottingham Leg Extensor Power Rig (Tiainen et al. 2005; Portegijs et al. 2009)

4.3.1 Bone measurements

Properties of the distal tibia and tibial shaft of the dominant leg (Studies I & II) or both legs (Studies III & IV) were determined by pQCT (XCT-2000, Stratec Medizintechnik, Pforzheim, Germany). The device was calibrated daily using the manufacturer-supplied standard phantom and monthly using a cone phantom. The distal tibia was defined as 5% and tibial shaft as 50% (Studies I & II) or 55% (Studies III & IV) of the measured tibial length proximal to the distal end plate. Tibial length was defined as the distance between the lateral malleolus and the lateral knee joint cleft. A planar scout view over the distal tibia joint line was acquired to adjust the scan line. A single axial slice was obtained with a voxel size of 0.8 mm, slice thickness of 2 mm, and scan speed of 20 mm/s.

In studies I and II, the images were analyzed with the Geanie software program (version 2.1; Commit Ltd., Espoo, Finland). The outer bone border was determined using a threshold of 169 mg/cm^3 for the distal tibia and 280 mg/cm^3 for the midshaft site. An automatic contour detection algorithm (K-mode) was chosen for the separation of cortical and trabecular bone. At the midshaft site, a threshold of 100 mg/cm^3 was applied to exclude bone marrow. At the distal site, bone marrow was included in the analyses. In studies III and IV, the pQCT images were analyzed with an automated threshold-free cortical bone detection method (the outer boundary detection and subsequent shrinking [OBS] procedure, OBS cortical bone detection 2.1) (Cervinka, Hyttinen & Sievänen 2012; Cervinka et al. 2015). The method was preferred over traditional density-based segmentation owing to the low cortical density and extremely thin cortices of the people with hip fracture, which could not be detected accurately by density thresholds (distinct or discontinued cortical edges in the analyzed images).

The bone variables analyzed are shown in Table 3. Compressive bone strength index (BSI) was calculated as $vBMD_{TOT}^2 \times CSA_{TOT}$ (Carter & Hayes 1976; Kontulainen et al. 2008). Maximal and minimal area (I_{maxA}, I_{minA}) and density-weighted (I_{maxD}, I_{minD}) moments of inertia reflect the bone's resistance to bending in the direction of the smallest and greatest flexural rigidity (Figure 4). Strength-strain index (SSI, density-weighted polar section modulus), reflects the bone's resistance to bending and torsional loads. Polar bone mass distribution was analyzed in Studies I and II. The analysis gives bone mineral mass as an angular distribution for 72 sectors around its center. The 5° steps were subsequently averaged into eight 45° sectors: anterior (A), anteromedial (A-M), medial (M), posteromedial (P-M), posterior (P), posterolateral (P-L), lateral (L) and anterolateral (A-L) (Figure 4). The coefficient of variation (CV) for the BMD, geometry, and strength index measurements in our laboratory ranges from 0.4% to 1.6% (Rantalainen et al. 2008).

TABLE 3 Bone variables reported in this study.

Bone site	Variable	Unit	Study
Distal tibia	BMC_{TOT}	mg/mm	I, II
	$vBMD_{TOT}$	mg/cm^3	III, IIV
	$vBMD_{TRAB}$	mg/cm^3	I, II
	CSA_{TOT}	mm^2	I, II, III
	BSI	g^2/cm^4	I, II, III, IV
Tibial midshaft	CSA_{CO}	mm^2	I, II
	CSA_{CO}/CSA_{TOT}	N/A	III
	Th_{CO}	mm	I
	BMC_{TOT}	mg/mm	I, II
	$vBMD_{CO}$	mg/cm^3	I, II, III, IV
	I_{maxD}	mg*cm	I, II
	I_{minD}	mg*cm	I, II
	I_{maxA}	mm^4	I
	I_{minA}	mm^4	I
	SSI	mm^3	III, IV
	BMC_{A}	mg/mm	I, II
	BMC_{A-M}	mg/mm	I, II
	BMC_{M}	mg/mm	I, II
	BMC_{P-M}	mg/mm	I, II
	BMC_{P}	mg/mm	I, II
	BMC_{P-L}	mg/mm	I, II
	BMC_{L}	mg/mm	I, II
	BMC_{A-L}	mg/mm	I, II

BMC_{TOT} = total bone mineral content; $vBMD_{TOT}$ = total volumetric bone mineral density; $vBMD_{TRAB}$ = trabecular vBMD; CSA_{TOT} = total cross-sectional area; BSI = compressive bone strength index; CSA_{CO} = cortical CSA; CSA_{CO}/CSA_{TOT} = ratio of cortical to total area; Th_{CO} = cortical thickness; I_{maxD}, I_{minD} = density-weighted maximal and minimal moments of inertia; I_{maxA}, I_{minA}, = maximal and minimal area moments of inertia; SSI = strength-strain index; A = anterior, A-M = anteromedial, M = medial, P-M = postero-medial, P= posterior, P-L = posterolateral, L = lateral, A-L = anterolateral; N/A = not applicable.

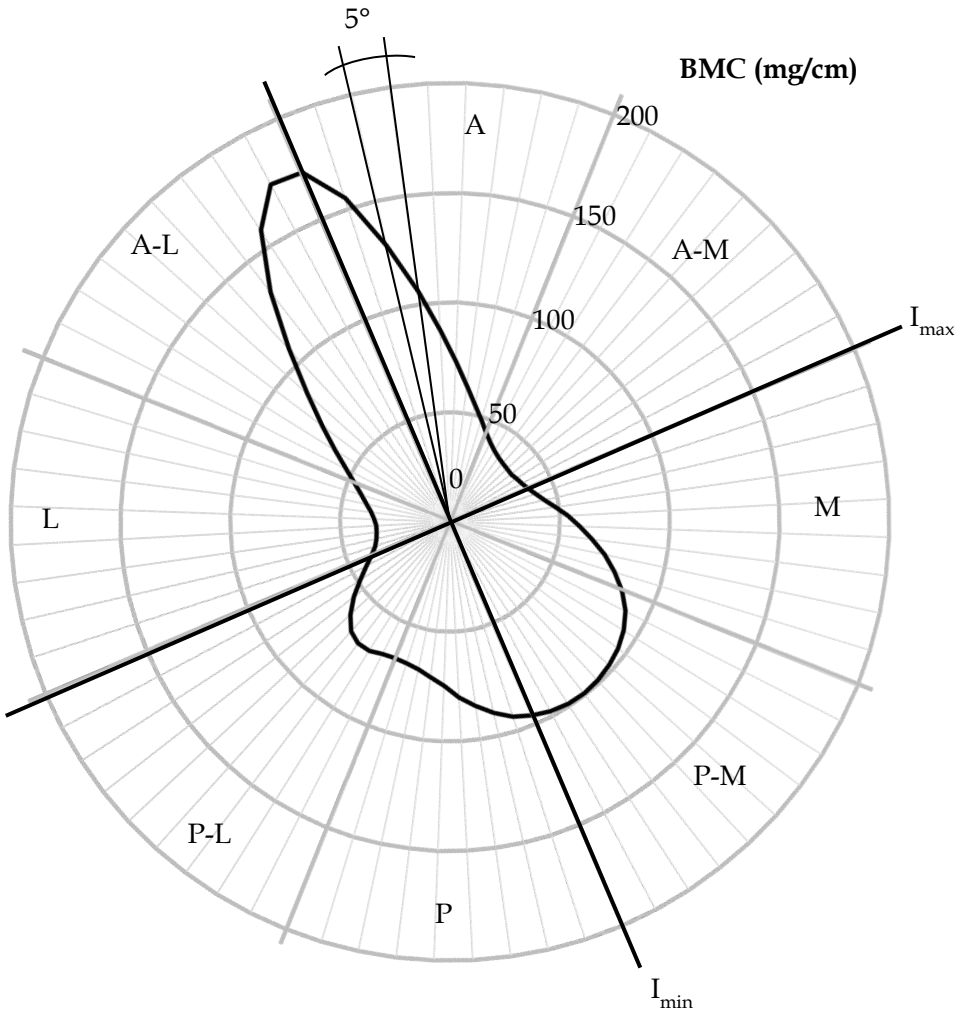

FIGURE 4 Cross-sectional image of tibial shaft showing the directions of the axes of the I_{max} and I_{min} moments and the mean polar mass distribution curve of the Athlas participants at baseline, indicating the angular distribution of bone mineral mass around the center of mass in 5° steps that were subsequently averaged into eight 45° sectors. (A = anterior, A-M = anteromedial, M = medial, P-M = posteromedial, P = posterior, P-L = posterolateral, L = lateral, A-L = anterolateral).

4.3.2 Health status and anthropometry

In the Athlas study (Studies I & II), the health history and current health of the participants, use of medical drugs, and injuries or diseases prohibiting physical training were assessed by a questionnaire and confirmed in a short interview and clinical examination. In the ProMo study (Studies III & IV), the presence of chronic medical conditions, use of prescription medications, fracture date and status, and type and date of surgery were obtained by a questionnaire, current prescriptions, and medical records, and confirmed in a medical examination. In the ProMo, blood count, C-reactive protein, and hemoglobin analyses were

performed to evaluate possible acute conditions before the performance measurements. Smoking history was assessed by a questionnaire.

Body height and weight were measured using a stadiometer and a balance beam scale (Studies I & II) or a digital scale (Studies III & IV). BMI was calculated as body weight divided by height squared (kg/m^2). Body fat percentage and lean body mass were assessed with bioimpedance devises [Spectrum II, RJL Systems, Detroit, MI, USA (Studies I & II) and BC-418, TANITA, Tokyo, Japan (Studies III & IV)].

4.3.3 Physical activity, physical performance and physical function

In the Athlas study (Studies I and II), current (during the preceding year, separated as indoor and outdoor seasons) and former training and competition performance were assessed with a detailed questionnaire, and confirmed in a short interview. At 10-year follow-up, the questionnaire also included questions about long-term training breaks or significant decreases in the volume of strength and sprint training during the 10-year period (Study II). In the ProMo study (Studies III & IV), current level of physical activity (PA) was assessed by a slightly modified Grimby scale (Grimby 1986) with the following response alternatives: 1) mainly resting, 2) most activities performed in a sitting position, 3) light PA twice a week at most, 4) moderate PA or housework approximately 3 hours a week, 5) moderate PA or housework at least 4 hours a week or heavy PA ≤4 hours a week, 6) physical exercise or heavy leisure time PA several times a week, and 7) competitive sports several times a week. The responses were re-categorized as inactivity (categories 1-2), light PA (category 3), and moderate-to-heavy PA (categories 4-7) (Turunen et al. 2017). In addition, physical exercise during the year preceding the fracture was assessed with a questionnaire. Rollator use at baseline was assessed with a questionnaire.

In the Athlas study, sprinting performance was assessed by 60-meter running times on an indoor synthetic track while wearing spiked shoes. The trial times were recorded by dual beam photocell gates. In the ProMo study, several methods were used to assess physical performance and physical function. The Short Physical Performance Battery (SPPB) includes habitual walking speed, chair rise, and balance tests (Guralnik et al. 1994). A higher score (range, 0 to 12) indicates better performance. Maximal isometric knee extension force of each leg was measured in a sitting position using an adjustable dynamometer chair (Good Strength; Metitur Ltd, Palokka, Finland) (Sipilä et al. 1996) (Study III). Leg extension power of each leg was measured in an upright sitting position using the Nottingham Leg Extensor Power Rig (Tiainen et al. 2005; Portegijs et al. 2009) (Study III). Perceived difficulty in walking outdoors was assessed by a questionnaire with five response categories: 1) no difficulties, 2) some difficulties, 3) a great deal of difficulties, 4) manage only with help, and 5) unable to manage even with help (Study IV).

4.4 Interventions and control conditions

4.4.1 High-intensity strength and sprint training program (Study I)

In the Athlas study (Study I), the experimental group received a 20-week training program combining sprint training with heavy and explosive strength exercises. The control participants were asked to continue their usual, mostly running-based, sprint training schedules. Researchers and coaches collaboratively designed the 20-week program and utilized also knowledge acquired from earlier studies in young adult athletes (e.g., Joch 1992; Delecluse et al. 1995; Kraemer & Häkkinen 2002). The program was designed to fit into the training and competitive seasons of the athletes. Although the main initial focus was to improve sprint performance and muscle strength, osteogenic characteristics were also considered. To reduce the potential for overtraining and injuries, and to optimize adaptation, the training was properly periodized. The program consisted of two 9- and 11-week periods that were further divided into three phases of 3–4 weeks with a different type, intensity, and volume of training (see Paper I, Supplementary Figure 1). Special attention was paid to sufficient volume and intensity of strength training, which was a novel training stimulus for the athletes.

Strength training, described in more detail in (Cristea et al. 2008), focused on the muscle groups important for sprinting such as leg extensors and hamstrings. The first phase consisted of strength endurance and hypertrophy exercises, while in the second and third phases, maximal strength training exercises alternated with explosive-type weightlifting and plyometrics. During the latter period, the three-phase protocol was repeated rather similarly with a progressive increase in training intensity and a decrease in training volume. Because of the wide age range of the participants, and the fact that most of them were not accustomed to heavy strength training, the intensity of the strength training program of the older participants (≥65 years) was in part planned to be slightly lower (lower resistance, more repetitions). The sprint training program was rather similar during both training periods, progressing from speed-endurance to maximum speed exercises with slight decreases in overall volume. Both the strength and sprint training session were undertaken twice weekly on non-consecutive days. The plyometric exercises were performed at the beginning of the speed training session, once or twice a week. Plyometric exercises progressed from lower-intensity double leg vertical jumps to higher-intensity horizontal bounding exercises.

The training programs, accompanied by written, pictorial and videotaped instructions for the exercises, were mailed to the participants in the experimental group. Both experimental and control participants were asked to fill out detailed training logs to monitor and record training adherence and progress and to enhance motivation for maximal effort. Field tests were organized every 5th week to obtain feedback on the athlete's training status and degree of progress.

Following completion of the study, the control participants also received the training program given to the experimental group.

4.4.2 Individually tailored multi-component home-based rehabilitation program (Study III)

In the ProMo study, the rehabilitation group participated in an individually tailored, yearlong, physical rehabilitation program aimed at restoring mobility and physical functional capacity (Sipilä et al. 2011; Salpakoski et al. 2014). The program consisted of an evaluation and modification of environmental hazards and guidance for safe walking, non-pharmacological pain management, motivational physical activity counseling, and a progressive home exercise program. The intervention was implemented in the participants' homes and included five to six home visits by a physiotherapist.

The individual home exercise program consisted of strengthening and stretching exercises for the lower limb muscles, balance training in the standing position, and functional training comprising stair climbing, indoor and outdoor walking, and reaching and turning in different directions. All the strengthening exercises were weight-bearing and included knee extension and flexion, hip abduction, plantar flexion, chair rising, and squatting. Progression was increased with resistance bands of three different strengths. The strengthening and stretching exercises (performed on the same day, three times per week), and the balance and functional exercises (performed on the same day, two to three times per week) were conducted on alternate days. Each training session lasted approximately 30 minutes. To promote progression, the program was updated four to five times with a more intensive and demanding protocol. Functional exercises were performed only during the first 12 weeks. All participants in the rehabilitation group kept a daily exercise diary. Motivational physical activity counseling comprised two face-to-face sessions (at three and six months) and three phone contacts (at four, eight, and 10 months).

Standard care

All participants received standard care. Based on participant interviews at baseline, 68% of the rehabilitation group and 71% of controls (p=0.813) had received a home exercise program from the hospital or the health care center before discharge to home. Typically, the program consisted of five to seven exercises for the lower limbs (mostly the fractured leg) without additional resistance or progression (Sipilä et al. 2011). Compliance with the home exercise program was not monitored. Control participants received standard care only and were asked to continue their daily living activities as usual.

4.5 Statistical methods

Descriptive analyses and the analyses in Study I were performed using SPSS software versions 22.0 and 24.0 (IBM, Armonk, NY, USA). Linear mixed models (Study II) and the robust linear regression models (Study IV) were analyzed using R version 3.5.1 (R core team, Vienna, Austria). In the linear mixed models, custom scripts utilizing the nlme package (version 3.1-148) and emmeans package (version 1.5.1) were used. General linear model (GLM) extended for MNAR (missing not at random) longitudinal data (Study III) was analyzed using Mplus 7.4. The significance level was set at 5% in all analyses.

4.5.1 Descriptive analyses

Mean values, standard deviations (SD) and standard errors (SE) were calculated using standard procedures. Baseline characteristics (and in Study II, also the 10-year follow-up physical and training characteristics) were compared by cross-tabulation and chi-square tests for discrete variables, by independent samples t-test for normally distributed data, and by the Mann-Whitney U test for non-normally distributed continuous data. The normality of the distributions was tested with the Shapiro-Wilk test. Mean changes were calculated as (follow-up - baseline), and mean percentage changes were calculated as [(follow-up - baseline)/baseline × 100]. Side-to-side differences in bone variables in Study III were defined as (nonfractured leg - fractured leg). Compliance with the intervention was calculated as (number of performed exercises)/(expected number of exercises) × 100.

4.5.2 Intervention effects

All outcome variables were analyzed according to intention-to-treat principles. In Study I, the effects of the strength and sprint training intervention were examined by means of repeated measures analysis of variance (RM-ANOVA). If the significance of the group-by-time interaction was $p<0.1$, an independent samples t-test was used to test the differences in percentage changes between the experimental and control groups. T-tests were performed for the whole study group, and separately in the two age groups [40–64 (experimental, n=21; control, n=14) and 65–85 (n=17 and 16, respectively) years]. The effect of the intervention was also examined by per protocol analysis including experimental participants who completed over 75% of the assigned strength and speed exercises.

In Study III, the effect of the rehabilitation intervention was assessed using an interaction term (group-by-time) in a general linear model for longitudinal data (Muthén & Muthén 2017). The models were adjusted for age. An additional analysis was performed by adjusting the models for age, sex, and body weight; however, but the results did not differ from the main analysis (data not shown). A per protocol analysis was undertaken with a subsample of rehabilitation group participants whose overall compliance with the physical exercises was over 70%

(n=16). In addition, sensitivity analyses, restricted to women, were performed (rehabilitation group, n=31; control group, n=32).

4.5.3 Longitudinal associations

4.5.3.1 Linear mixed models

In Study II, the association of continued strength and sprint training with 10-year longitudinal changes in bone outcomes was assessed using an interaction term (group × time) in linear mixed models. The models were adjusted for age. The mean percentage changes shown in the figures were calculated from the estimated group means. In cases where the significance of the group-by-time interaction was $p<0.05$, the mean percentage changes are also shown as differences in changes between the well-trained and less-trained athletes. The percentage changes were also calculated separately for two age groups [40-64 (well-trained, n=21; less-trained, n=18) and 65-85 (n=15 and 15, respectively) years]. Adjustment for multiple testing was performed by utilizing a method introduced by Cheverud (2001) that replaces the observed number of tests with the effective number of tests. The method takes into account the correlation of the variables so that the higher the correlation the lower the effective number of tests. As the focus was on changes over time (interactions), the correlation matrix for follow-up differences was utilized. Data are presented as mean values and 95% confidence intervals (CI) (Model I, raw p-values) and additionally with CIs with alpha-level adjustment for 17 simultaneous tests for the main analysis (Model II).

4.5.3.2 Regression models

In Study IV, the associations of physical function and LBM with longitudinal changes in bone outcomes were assessed with a robust linear regression approach (Venables & Ripley 1999). The method down-weights the influence of extreme outliers, and hence reduces the sample size but provides more reliable regression coefficients. Depending on the outcome variable, the sample size reduction due to weighting ranged from 5 to 10%. The mean percentage changes in vBMD and bone strength indices were used as dependent variables. Baseline LBM, SPPB score and the ability to walk outdoors were entered at the same time as predictors in the models. The SPPB scores were recoded into a single binary variable: 0) high performance (score ≥7) or 1) low performance (score <7). A score below 7 indicates a high risk for disability (Guralnik et al. 1995). The categories in perceived difficulty in walking outdoors were recoded as: 0 = major difficulties or unable (categories 3-5), or 1 = no difficulties or minor difficulties (categories 1-2). The models were adjusted for age, gender, number of chronic diseases, surgical procedure (internal fixation vs. hemiarthroplasty vs. total arthroplasty) and use of bisphosphonate medication (yes/no) at baseline.

4.5.4 Missing data

In the Athlas study, the amount of missing data was minor. In the experimental study (Study I), missing values in outcomes were solely due to dropout (n=4). Hence, in that study we used RM-ANOVA that utilizes information from complete pairs only. In the 10-year follow-up (Study II), one participant was removed from the mid-tibia analysis owing to movement artifact.

In the ProMo study, the amount of missing data was considerable. With 81 subjects scanned in both legs, the target number of scans per bone site at each time point was 162. For the distal tibia, 154 valid scans were obtained at baseline, 133 at 3 months, 137 at 6 months, and 130 at 12 months. For the midshaft site, the corresponding numbers were 156, 136, 134, and 130. The main reasons for the missing bone data in the ProMo study were inability to perform the measurements, inaccurate positioning of the leg, a technically invalid pQCT scan, substantial movement artifacts, and metal in tissues in the scanned region. In Study III, partly because of the frailty of the subjects, we assumed that data were missing-not-at-random (MNAR). Hence, we used the maximum likelihood-based pattern-matching model (Enders 2010) to include the estimated data from dropouts in the statistical data analysis up to the time of loss to follow-up. In the regression analyses (Study IV), predictive mean matching of the mice package (van Buuren & Groothuis-Oudshoorn 2011) in the R programming environment was used to impute missing values for lean body mass in three subjects.

5 RESULTS

5.1 Participant characteristics

Tables 4-6 summarize the background characteristics of the study subjects. At baseline, no differences were observed between the intervention and control groups (Studies I & III) or the groups of well-trained and less-trained athletes (Study II) except in the frequency of strength training, which was significantly higher in the well-trained compared to less-trained group (Table 4). At the 10-year follow-up, the well-trained and less-trained groups differed in their training habits (Table 4).

Sixty-two of the Athlas athletes participated in both the RCT and the 10-year follow-up. Seven athletes who had been excluded from the RCT attended the follow-up measurements while ten athletes participated in the RCT but not in the follow-up (Figure 2). The mean age of the athletes participating in the Athlas study (intervention or follow-up, n=79) was 61.5 (SD 11.9) whereas in ProMo the mean age was 80.0 (7.1). In the Athlas athletes, mean training years at baseline was 32 (16). Mean training frequency during the year preceding the intervention was 4.3 (1.3) sessions/week. The training programs mainly consisted of sprint training, speed-endurance training, and plyometric exercises. Strength training was performed by 78% of the athletes. In the ProMo study, 88% of the patients with hip fracture reported taking part in physical exercise of any kind during the year preceding the fracture. The most common activities were walking (reported by 44% of the participants), cycling (19%), gymnastics (15%), Nordic walking (12%) and swimming (11%). Gym training was performed by 6% of the ProMo participants. During the month preceding the intervention, however, over 90% of the ProMo participants reported being inactive or doing only light physical activity (Table 4). At baseline, 52% of the ProMo participants had a SPPB score below seven, which indicates a high risk for disability (Guralnik et al. 1995).

TABLE 4 Baseline characteristics of the masters athletes (Studies I & II) and older adults with hip fracture (Studies III & IV) and 10-year follow-up characteristics of the masters athletes (Study II).

	Athlas						ProMo	
	Study I		Study II				Studies III & IV	
	Experimental (n=40)	Control (n=32)	Well-trained (n=36)		Less-trained (n=33)		Rehabilitation (n=40)	Control (n=41)
			Baseline	10-yr	Baseline	10-yr		
Age, years	60.2 (11.8)	61.8 (12.1)	60.8 (9.5)	70.6 (9.4)	60.5 (12.7)	70.4 (12.7)	80.9 (7.7)	79.1 (6.4)
Height, cm	175 (6)	173 (7)	174 (6)	173 (6)	176 (6)	175 (7)	161 (9)	160 (9)[i]
Weight, kg	73.2 (7.5)	73.8 (9.0)	73.6 (7.0)	73.2 (7.9)	73.4 (7.8)	74.5 (8.8)	65.8 (11.9)	65.8 (11.3)
Lean body mass, kg	63.3 (5.6)	62.7 (7.8)	63.2 (6.4)	62.1 (5.9)[c]	62.9 (5.8)	61.5 (6.5)[d]	44.9 (8.1)[g]	44.0 (8.7)[g]
Body fat, %	13.6 (4.1)	15.0 (4.0)	14.8 (4.3)	15.0 (4.5)[c]	14.1 (4.6)	15.5 (4.3)[d]	30.5 (7.1)[g]	32.2 (5.8)[g]
Current bisphosphonate use, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (23)	7 (17)
Smoking, n (%)								
Former	N/A	N/A	6 (17)	6 (17)	6 (18)	6 (18)	4 (10)	6 (15)
Current	N/A	N/A	1 (3)	1 (3)	0 (0)	0 (0)	2 (5)	5 (12)
Level of physical activity, n (%)								
Inactivity (mostly sitting)	N/A	N/A	N/A	N/A	N/A	N/A	15 (38)	11 (28)
Light activity	N/A	N/A	N/A	N/A	N/A	N/A	23 (58)	25 (63)
Moderate to heavy activity	N/A	N/A	N/A	N/A	N/A	N/A	2 (5)	4 (10)
Running and plyometrics, times/wk	3.0 (1.5)[a]	2.9 (1.3)	3.4 (1.5)	2.1 (0.6)	2.9 (1.6)[e]	0.8 (1.3)	N/A	N/A
Strength training, times/wk	0.8 (0.6)[a]	1.0 (0.8)	1.1 (0.7)	1.4 (0.7)	0.6 (0.6)[e]	0.7 (1.1)	N/A	N/A
60 m sprint time	8.50 (0.87)[a]	8.45 (0.70)	8.36 (0.58)[b]	9.32 (1.09)[d]	8.63 (0.94)	9.94 (2.45)[f]	N/A	N/A
Knee extension force$_{fractured}$, N	N/A	N/A	N/A	N/A	N/A	N/A	185 (73)[b]	168 (72)[i]
Knee extension force$_{non\text{-}fractured}$, N	N/A	N/A	N/A	N/A	N/A	N/A	240 (93)[g]	228 (84)[i]
Leg extension power$_{fractured}$, W	N/A	N/A	N/A	N/A	N/A	N/A	56 (29)[e]	51 (29)[g]
Leg extension power$_{non\text{-}fractured}$, W	N/A	N/A	N/A	N/A	N/A	N/A	74 (37)[h]	74 (41)[a]
SPPB score (range, 0-12)	N/A	N/A	N/A	N/A	N/A	N/A	5.8 (2.5)	6.6 (2.2)
Walking outdoors, n (%)								
No/minor difficulties	N/A	N/A	N/A	N/A	N/A	N/A	22 (55)	28 (68)
Major difficulty/unable	N/A	N/A	N/A	N/A	N/A	N/A	18 (45)	13 (32)
Rollator use, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	24 (60)	25 (61)

Values are means (SD) or n (%). SPPB = Short Physical Performance Battery. [a] n=39, [b] n=34, [c] n=31, [d] n=25, [e] n=32, [f] n=16, [g] n=38 [h] n=36, [i] n=40.

Among the participants accepted for the Athlas trial (Study I), 14 (19%) presented with chronic conditions (asthma, n=3; celiac disease, n=1; hypertension, n=7; hypothyroidism, n=2; type 1 diabetes, n=1). However, all conditions had been adequately diagnosed by their own physician and thereafter treated with good response. During the 10-year follow-up (Study II), three participants in the well-trained and three in less-trained groups presented with prostate cancer. All athletes were free of other diseases that could affect bone, such as rheumatoid arthritis, celiac disease, or colitis ulcerosa. In the ProMo study, the average number of chronic conditions in both the rehabilitation and control groups was 3 (SD 2). The groups did not differ in their hip fracture- and surgery-related characteristics (Table 5).

TABLE 5 Hip fracture- and surgery-related characteristics of the ProMo participants at baseline.

	Rehabilitation group (n=40)	Control group (n=41)
Time since fracture (days)	68 (16)	71 (37)
Site of fracture, n (%)		
Femoral neck	27 (68)	25 (61)
Pertrochanteric	13 (33)	16 (39)
Type of surgery, n (%)		
Internal fixation	19 (48)	19 (46)
Hemiarthroplasty	15 (38)	18 (44)
Total arthroplasty	6 (15)	4 (10)

Values are means (SD) or n (%).

Selected bone characteristics of the athletes and the patients with hip fracture are summarized in Table 6. Due to the use of different pQCT image analysis methods, the bone results of the different study projects are not fully comparable. Overall, the OBS method tends to give slightly higher values for cortical area and lower values for cortical density. Figure 5 illustrates the differences in bone properties between masters athletes (strong bone structure) and older adults with hip fracture (fragile bone structure) representing the opposite ends of the physical activity, physical performance, and bone health spectrums at later adult ages. The figure illustrates the variations found in the bone density, shape, and cortical thickness of these two study populations, complemented with comparisons between participants of similar age, sex, and body height.

TABLE 6 Selected bone characteristics of the participants.

	Athlas		ProMo					
	Study I	Study II	Studies III & IV					
			Fractured leg			Non-fractured leg		
			All	Women	Men	All	Women	Men
Distal tibia	(n=72)	(n=69)	(n=76)	(n=60)	(n=16)	(n=78)	(n=60)	(n=18)
CSA_{TOT}	1201	1204	1022	980	1179	1039	993	1193
(mm^2)	(147)	(154)	(164)	(144)	(141)	(164)	(137)	(154)
$vBMD_{TOT}$	355	354	215	203	263	218	205	259
(mg/mm^3)	(47)	(44)*	(52)	(45)	(49)	(52)	(46)	(49)
BSI	1.53	1.52	0.50	0.41	0.82	0.51	0.43	0.81
(g^2/cm^4)	(0.40)	(0.39)	(0.25)	(0.17)	(0.24)	(0.25)	(0.17)	(0.25)
Tibial midshaft	(n=72)	(n=69)	(n=78)	(n=60)	(n=18)	(n=78)	(n=60)	(n=18)
CSA_{CO}	415	416	244	220	327	248	221	337
(mm^2)	(50)	(48)	(62)*	(45)*	(35)*	(64)*	(41)*	(39)*
$vBMD_{CO}$	1094	1095	1043	1028	1095	1045	1029	1098
(mg/mm^3)	(26)	(25)	(71)	(68)	(52)	(78)	(80)	(37)

Values are means (SD). *previously unpublished data. Studies I & II: density threshold-based segmentation (Geanie software), Studies III & IV: threshold-free segmentation (OBS procedure). CSA_{TOT} = total cross-sectional area; $vBMD_{TOT}$ = total volumetric bone mineral density, BSI = compressive bone strength index CSA_{CO} = cortical CSA, $vBMD_{CO}$ = cortical vBMD.

5.2 Intervention adherence and adverse events (Studies I & III)

In Athlas (Study I), two experimental group participants withdrew from the study due to persistent musculoskeletal pain caused by a pre-existing sports injury (unrelated to the exercise intervention). Two controls dropped out for personal reasons. In ProMo (Study III), one rehabilitation group participant and two controls withdrew from the study for personal reasons, and one rehabilitation group participant died from cardiac failure unrelated to the intervention. No intervention-related adverse events occurred in either of the studies. In the Athlas study, some participants in both the experimental (n=16) and control (n=9) reported minor musculoskeletal discomfort (transient muscle strains and joint sprains) during testing, training, and competitions. However, all were able to continue their training after a few days or weeks of modified or discontinued training. In the ProMo study, four rehabilitation group participants were suspended by a physician for medical reasons during the first six months. Two of them returned to the intervention (revision operation, femoral fracture), but two were unable to continue (pneumonia and a new hip fracture, pulmonary embolism). During the final six months, five participants were suspended and none returned (pubic bone fracture, urinary tract infection, cerebral infarction, cardiac failure, sacrum strain fracture). In the control group, four revision operations were performed, and no new hip fractures occurred.

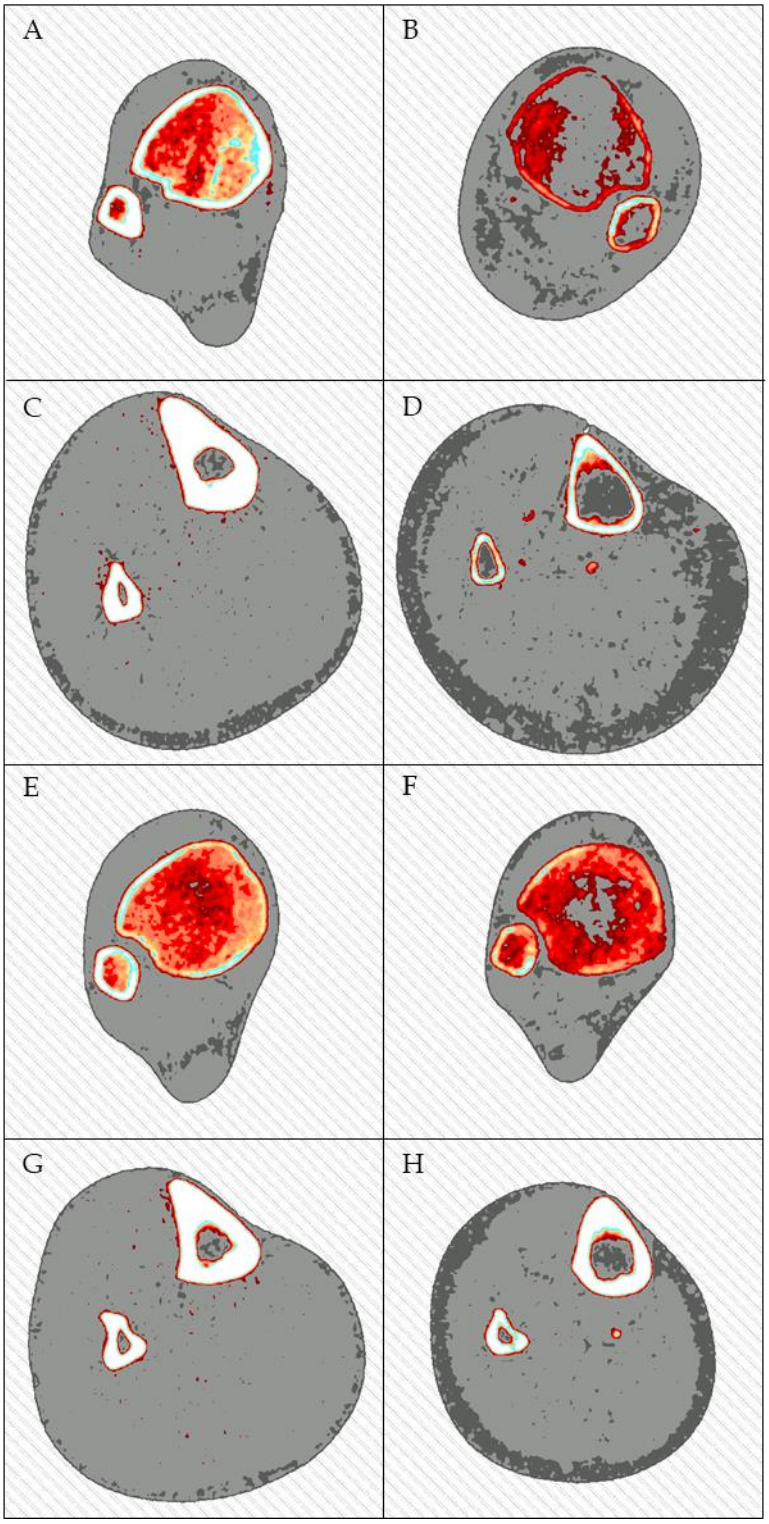

FIGURE 5 PQCT images of distal tibia (A, B, E, F) and tibial midshaft (C, D, G, H) showing the superior bone mass and cortical thickness of a master athlete from the Athlas study (left panel) compared to an older adult with hip fracture from the ProMo study (right panel). In the lower panels (E-H), the participants of the different studies are matched for age, sex and body height. Different colors indicate different volumetric density values (from low to high density: red-yellow-white).

5.3 Compliance with physical exercises (Studies I & III)

In the Athlas study (Study I), the overall training adherence rate was 64% [23 (SD11) sessions] for strength training, 69% [27 (12) sessions] for sprint training and 52% [17 (10) sessions] for the plyometric exercises. The control group continued their own habitual training regimen, which included 19 (10) strength training sessions, 30 (14) sprint training sessions and 11 (12) plyometric exercise sessions. The strength training of the controls comprised mainly strength endurance and hypertrophy exercises. The number of active training weeks varied across the experimental and control groups [17 (4.6) and 18 (2.8), respectively]. During the active weeks, the experimental participants reported a significantly higher average number of strength [1.3 (0.5) vs. 1.0 (0.5), p=0.034] and plyometric training sessions [0.9 (0.5) vs. 0.6 (0.6), p=0.035] than controls.

In the ProMo study (Study III), overall compliance with the home exercises was 50% for the strengthening, 45% for the stretching, and 54% for the balance exercises. During the first six months, the corresponding values were 61%, 53%, and 65% and during the last 6 months 39%, 37%, and 43%. Overall compliance with the functional exercises during the first 12 weeks was 69%. Compliance with the physical activity counseling sessions ranged from 97% (first face-to-face session) to 79% (third phone contact).

5.4 Effects on physical function and physical performance (Studies I & III)

In the Athlas study, 60-meter sprint times improved in the experimental group whereas in controls they declined over the 20-week intervention (group × time interaction p=0.025). The yearlong ProMo rehabilitation intervention had no effect (group × time) on maximal isometric knee extension force or leg extension power of the patients with hip fracture. Muscle force of the fractured leg and leg extension power of both legs increased significantly over time in both the rehabilitation and control groups (time effect, 12 months, $p<0.001$).

5.5 Intensive exercise and bone during aging (Studies I & II)

Tables 7 and 8 and Figures 6 and 7 summarize the bone results of the athlete studies by showing the effects of high-intensity strength and sprint training (Study I), and the associations of maintained training with the 10-year longitudinal changes (Study II) in bone traits. No differences were found in baseline bone characteristics between the experimental and control groups (Study I) or between the groups of well-trained and less-trained athletes (Study

II) except for $vBMD_{CO}$ of the mid-tibia (Study I), which was significantly higher in the experimental group compared to controls (p=0.002).

5.5.1 Effects of high-intensity strength and sprint training program on tibial bone traits (Study I)

The 20-week strength and sprint training intervention had no effect on distal tibia bone traits (Table 7). The effect of the training on the tibial midshaft is shown in Tables 7 and 8, and in Figures 6 and 7. In the experimental group compared controls, Th_{CO} increased by 2.0% (p=0.007) and I_{minA} by 1.9% (p=0.034) (Figure 6). In the group aged 65-85 (experimental, n=17; control, n=16), the corresponding difference in change in favor of the experimental group was 2.8% for Th_{CO} (p=0.008) (Figure 7). In the group aged 40-64 (n=21 and 14, respectively), the increase in I_{minA} in favor of the experimental participants was 2.8% (p=0.031) (Figure 7).

Per protocol analysis: No intervention effect was observed in distal tibia bone traits (Table 7). The effect of the training on the tibial midshaft bone traits is shown in Tables 7 and 8, and in Figure 6. The average difference in change in favor of the experimental group was 1.8% for CSA_{CO} (p=0.007) and 2.6% for Th_{CO} (p=0.012). In the experimental group compared to controls, I_{minA} increased by 3.2% (p=0.006) and I_{minD} by 1.8% (p=0.023). The corresponding increase in BMC_{TOT} was 0.7% (p=0.017), whereas the change in $vBMD_{CO}$ favored the control participants (0.8%, p=0.043). The polar mass distribution analysis revealed a significant group × time interaction at the A-M site (Table 8) reflecting 2.2% difference in change in favor of the experimental group (p=0.051).

TABLE 7 Effects of strength and sprint training on tibial bone traits (Study I) and associations of continued training with longitudinal changes in tibial bone traits (Study II) of the masters athletes.

		Experimental[a] (n=38)		Experimental[b] (n=16)		Control (n=30)		Well-trained (n=36)		Less-trained (n=32)		Group × time			
												RCT[c]		10-yr follow-up[d]	
		BL	20 wk	BL	20 wk	BL	20 wk	BL	10 yr	BL	10 yr	ITT	PP	Model 1	Model 2
5%	BMC_{TOT} (mg/mm)	429 (68)	426 (67)	431 (70)	426 (69)	419 (66)	417 (63)	427 (64)	425 (65)	420 (70)	405 (73)	0.705	0.245	**0.019**	0.250
	CSA_{TOT} (mm^2)	1204 (139)	1192 (130)	1212 (153)	1189 (140)	1204 (156)	1200 (143)	1195 (139)	1192 (132)	1215 (172)	1208 (175)	0.548	0.257	0.743	1.000
	$vBMD_{TRAB}$ (mg/cm^3)	311 (34)	311 (34)	310 (35)	311 (26)	303 (44)	303 (44)	315 (39)	314 (41)	300 (38)	291 (43)	0.794	0.439	**0.003**	**0.044**
	BSI (g^2/cm^4)	1.55 (0.38)	1.54 (0.38)	1.56 (0.42)	1.55 (0.42)	1.49 (0.42)	1.49 (0.42)	1.55 (0.39)	1.54 (0.41)	1.48 (0.39)	1.39 (0.40)	0.995	0.554	**0.013**	0.180
50%	BMC_{TOT} (mg/mm)	511 (59)	513 (58)	504 (69)	508 (68)	504 (62)	505 (62)	4920 (1004)	5013 (1281)	5012 (1301)	5072 (1291)	0.211	**0.020**	**0.024**	0.250
	CSA_{CO} (mm^2)	416 (48)	418 (47)	408 (57)	413 (56)	414 (52)	413 (54)	416 (50)	416 (46)	415 (46)	410 (51)	0.071	**0.008**	**0.006**	0.083
	Th_{CO} (mm)	5.35 (0.64)	5.39 (0.63)	5.31 (0.61)	5.39 (0.63)	5.27 (0.74)	5.20 (0.75)	-	-	-	-	**0.008**	**0.010**	-	-
	$vBMD_{CO}$ (mg/cm^3)	1103 (20)	1102 (19)	1109 (20)	1103 (17)	1085 (26)	1088 (22)	1783 (384)	1849 (430)	1861 (431)	1862 (459)	0.137	**0.039**	0.617	1.000
	I_{maxA} (mm^4)	47320 (11300)	47590 (11050)	46533 (14728)	47249 (14404)	48220 (12030)	48350 (12240)	-	-	-	-	0.675	0.181	-	-
	I_{minA} (mm^4)	17520 (4137)	17800 (4210)	16719 (4188)	17178 (4137)	18550 (3774)	18530 (3894)	-	-	-	-	**0.041**	**0.012**	-	-
	I_{maxD} (mg*cm)	4959 (1210)	4980 (1176)	4913 (1619)	4957 (1569)	4967 (1280)	4989 (1291)	508 (58)	511 (58)	511 (58)	506 (61)	0.947	0.405	0.109	.822
	I_{minD} (mg*cm)	1792 (425)	1813 (426)	1725 (442)	1757 (435)	1858 (385)	1862 (392)	1095 (24)	1096 (26)	1096 (26)	1097 (30)	0.105	**0.038**	0.852	1.000

Values are means (SD). [a] Intention-to-treat (ITT) analysis, [b] per protocol analysis (PP), [c] RM-ANOVA, [d] linear mixed models. Model 1: raw p-values, model 2: adjusted for multiple testing. BMC_{TOT} = total bone mineral content; CSA_{TOT} = total cross-sectional area; BSI = compressive bone strength index CSA_{CO} = cortical CSA; Th_{CO} = cortical thickness; I_{maxA}, I_{minA} = maximal and minimal area moments of inertia; $vBMD_{CO}$ = cortical volumetric bone mineral density; I_{maxD}, I_{minD} = density-weighted maximal and minimal moments of inertia.

TABLE 8 Effects of strength and sprint training on polar mass distribution of the tibial midshaft (Study I) and associations of continued training with longitudinal changes in tibial midshaft bone traits (Study II) of the masters athletes.

BMC (mg/mm)	Experimental[a] (n=38)		Experimental[b] (n=16)		Control (n=30)		Well-trained (n=36)		Less-trained (n=32)		p-value (Group × time) RCT[c]		10-yr follow-up[d]	
	BL	20 wk	BL	20 wk	BL	20 wk	BL	10 yr	BL	10 yr	ITT	PP	Model 1	Model 2
A	895 (130)	899 (128)	890 (124)	908 (141)	881 (157)	879 (153)	913 (121)	943 (139)	894 (133)	891 (147)	0.636	0.247	**0.017**	0.225
A-M	336 (65)	339 (66)	329 (64)	336 (65)	342 (63)	341 (63)	344 (66)	346 (63)	349 (61)	342 (63)	0.208	**0.046**	0.077	0.698
M	491 (110)	494 (108)	469 (106)	471 (103)	514 (99)	512 (99)	476 (81)	474 (82)	495 (94)	487 (100)	0.319	0.523	0.419	1.000
P-M	878 (141)	877 (135)	852 (133)	851 (123)	816 (161)	822 (159)	860 (146)	861 (155)	856 (152)	846 (139)	0.245	0.317	0.283	0.993
P	723 (142)	728 (145)	736 (187)	747 (192)	732 (148)	729 (145)	728 (150)	754 (152)	740 (135)	728 (146)	0.253	0.121	**<0.001**	**0.007**
P-L	551 (99)	551 (96)	531 (77)	537 (80)	547 (86)	547 (88)	563 (88)	561 (96)	554 (101)	549 (105)	0.854	0.479	0.678	1.000
L	330 (64)	334 (64)	320 (46)	324 (47)	325 (68)	327 (70)	321 (55)	315 (54)	327 (60)	318 (60)	0.672	0.689	0.590	1.000
A-L	910 (168)	910 (891)	913 (208)	905 (191)	888 (133)	891 (144)	877 (123)	872 (115)	892 (129)	897 (122)	0.781	0.470	0.518	1.000

Values are means (SD). [a] Intention-to-treat (ITT) analysis, [b] per protocol analysis (PP), [c] RM-ANOVA, [d] linear mixed models, adjusted for age. Model 1: raw p-values, model 2: adjusted for multiple testing. Bone mineral content (BMC)–values (mg/cm) are sum values of nine 5° sectors. BL= baseline. (A anterior, A-M anteromedial, M medial, P-M posteromedial, P posterior, P-L posterolateral, L lateral, A-L anterolateral).

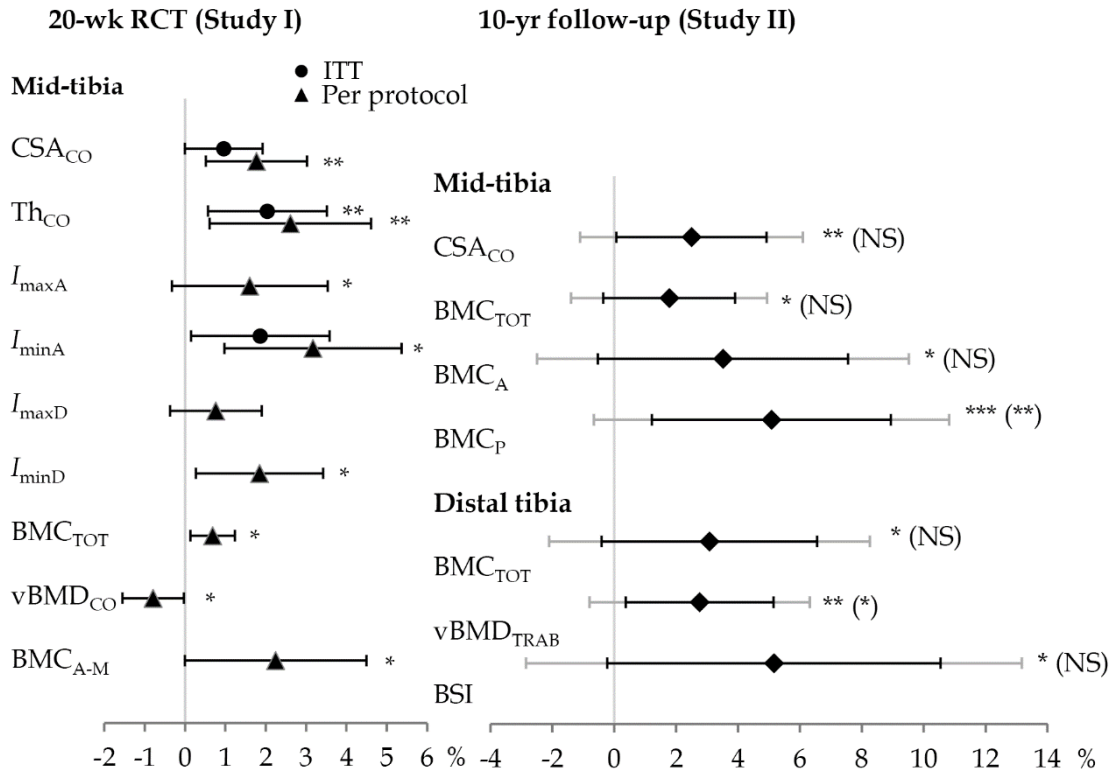

FIGURE 6 Differences in changes in the tibial bone traits of the athletes after 20 weeks (*left panel*) or 10 years (*right panel*) of high-intensity strength and sprint training. Experimental group vs. control group (*left panel*) or well-trained vs. less-trained (*right panel*) (mean, 95% confidence interval). Intention-to-treat (ITT) and per protocol analysis *(left panel*). Grey lines show multiple test corrected confidence intervals. p-values for group × time (RM-ANOVA/linear mixed models). * p≤0.05; ** p≤0.01, *** p≤0.001; adjusted p-values in parentheses.

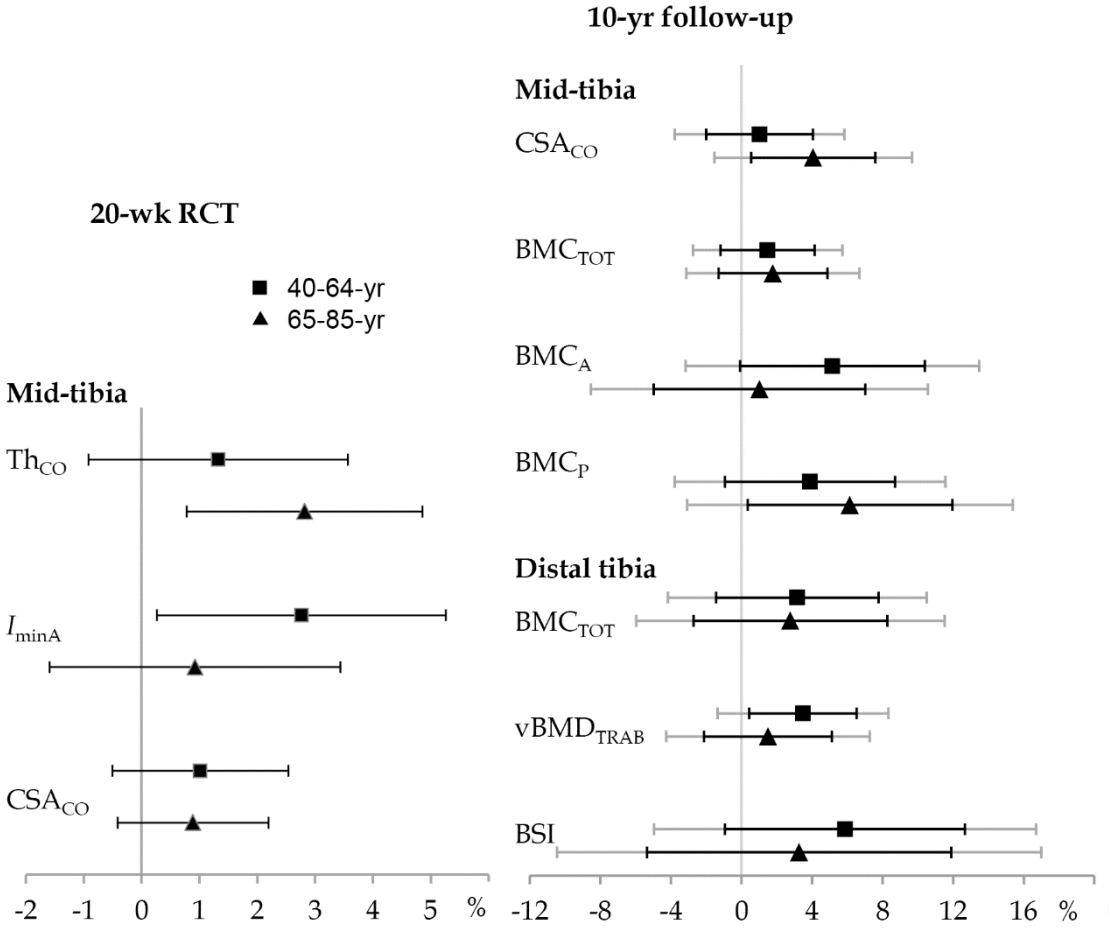

FIGURE 7 Differences in changes in the tibial bone traits of the athletes after 20 weeks (*left panel*) or 10 years (*right panel*) of high-intensity strength and sprint training among age groups. Experimental group vs. control group (*left panel*) or well-trained vs. less trained (*right panel*) (mean, 95% confidence interval). Grey lines show multiple test corrected confidence intervals.

5.5.2 Associations of regular strength and sprint training with bone aging (Study II)

The associations of continued strength and sprint training with changes in distal tibia bone traits are shown in Table 7 and in Figures 6-8. A significant group × time interaction ($p<0.05$, raw values) was found for BMC_{TOT}, $vBMD_{TRAB}$ and BSI_{COMP}, reflecting the maintained bone properties in the well-trained and the decreased bone properties in the less-trained athletes over the 10-year period (Figure 8). The mean difference in change in favor of the well-trained was 3.1% for BMC_{TOT}, 2.8% for $vBMD_{TRAB}$, and 5.2% for BSI_{COMP} (Figure 6). After adjustment for multiple testing, the difference in $vBMD_{TRAB}$ between the groups remained significant. In the group aged 40-64, the differences in change favoring the well-trained were 3.2% in BMC_{TOT}, 3.5% in $vBMD_{TRAB}$, and 5.9% in BSI (5.9%) (Figures 7 and 10).

The associations of continued strength and sprint training with the changes in tibial midshaft bone traits are shown in Tables 7 and 8 and in Figures 6-9. A significant group × time interaction ($p<0.05$, raw values) was found for CSA_{CO}, BMC_{TOT}, BMC_A and BMC_P. This reflected the increase in these parameters in the well-trained and the decrease or no change in the same parameters in the less-trained athletes over the follow-up (Figures 8 and 9). In the well-trained compared to less trained athletes, CSA_{CO} increased by 2.5%, BMC_{TOT} by 1.8%, BMC_A by 3.5% and BMC_P by 5.1% (Figure 6). After adjustment for multiple testing, BMC_P remained significant. In the group aged 40-64, the difference in change in favor of the well-trained was 5.2% in BMC_A and 3.9% in BMC_P (Figure 7). Among the 65- to 85-year-olds, the overall difference in change at follow-up, combining the increase in the well-trained and the decrease in less-trained athletes, was 4.1% in CSA_{CO} and 6.2% in BMC_P (Figures 7 and 10).

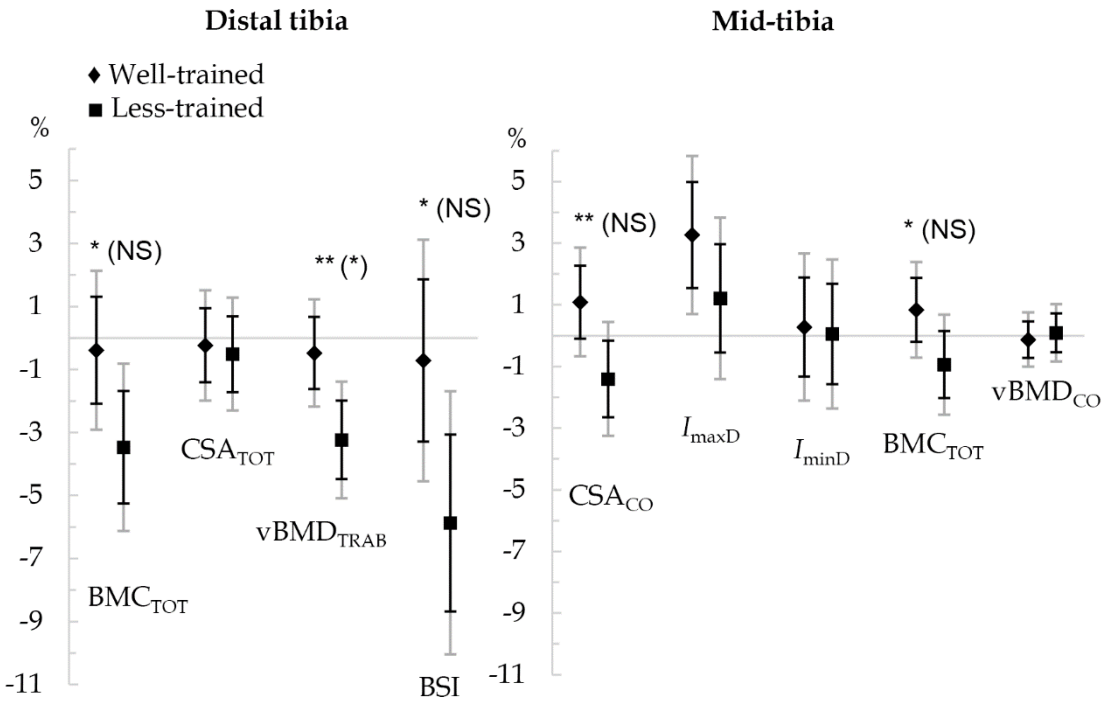

FIGURE 8 10-year percentage changes in tibial outcomes of the well-trained and less-trained athletes (mean, 95% confidence interval). Black lines show unadjusted confidence intervals and grey lines multiple test corrected confidence intervals. The displayed p-values denote the unadjusted group × time interaction effect $p<0.05$. Adjusted p-values in parentheses. * $p\leq0.05$; ** $p\leq0.01$, *** $p\leq0.001$.

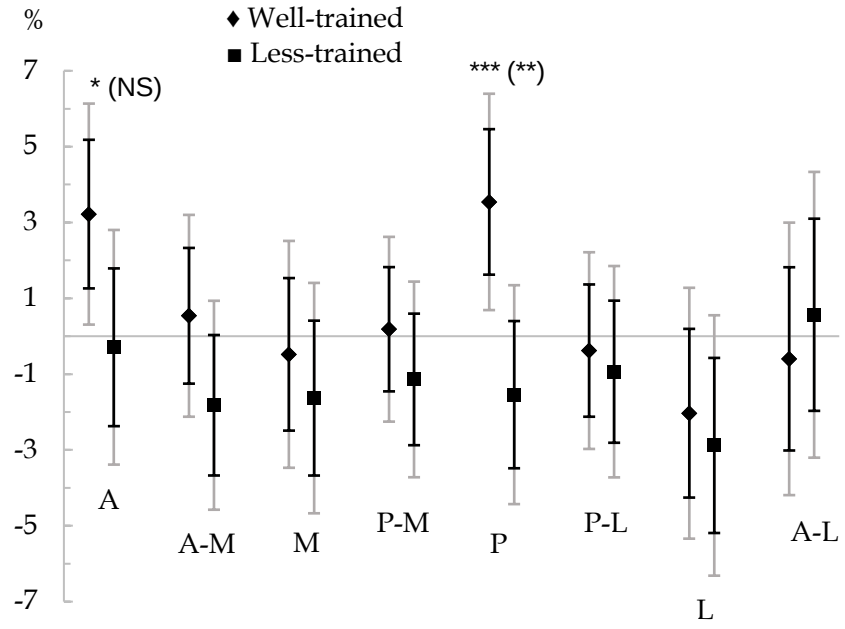

FIGURE 9 10-year percentage changes in polar mass distribution of the tibial midshaft of the well-trained and less-trained athletes (mean, 95% confidence interval). Black lines show unadjusted confidence intervals and grey lines multiple test corrected confidence intervals. The displayed p-values denote the unadjusted group × time interaction effect $p<0.05$. Adjusted p-values in parentheses. * $p\leq0.05$; ** $p\leq0.01$, *** $p\leq0.001$. (A = anterior, A-M = anteromedial, M = medial, P-M = posteromedial, P = posterior, P-L = posterolateral, L = lateral, A-L = anterolateral).

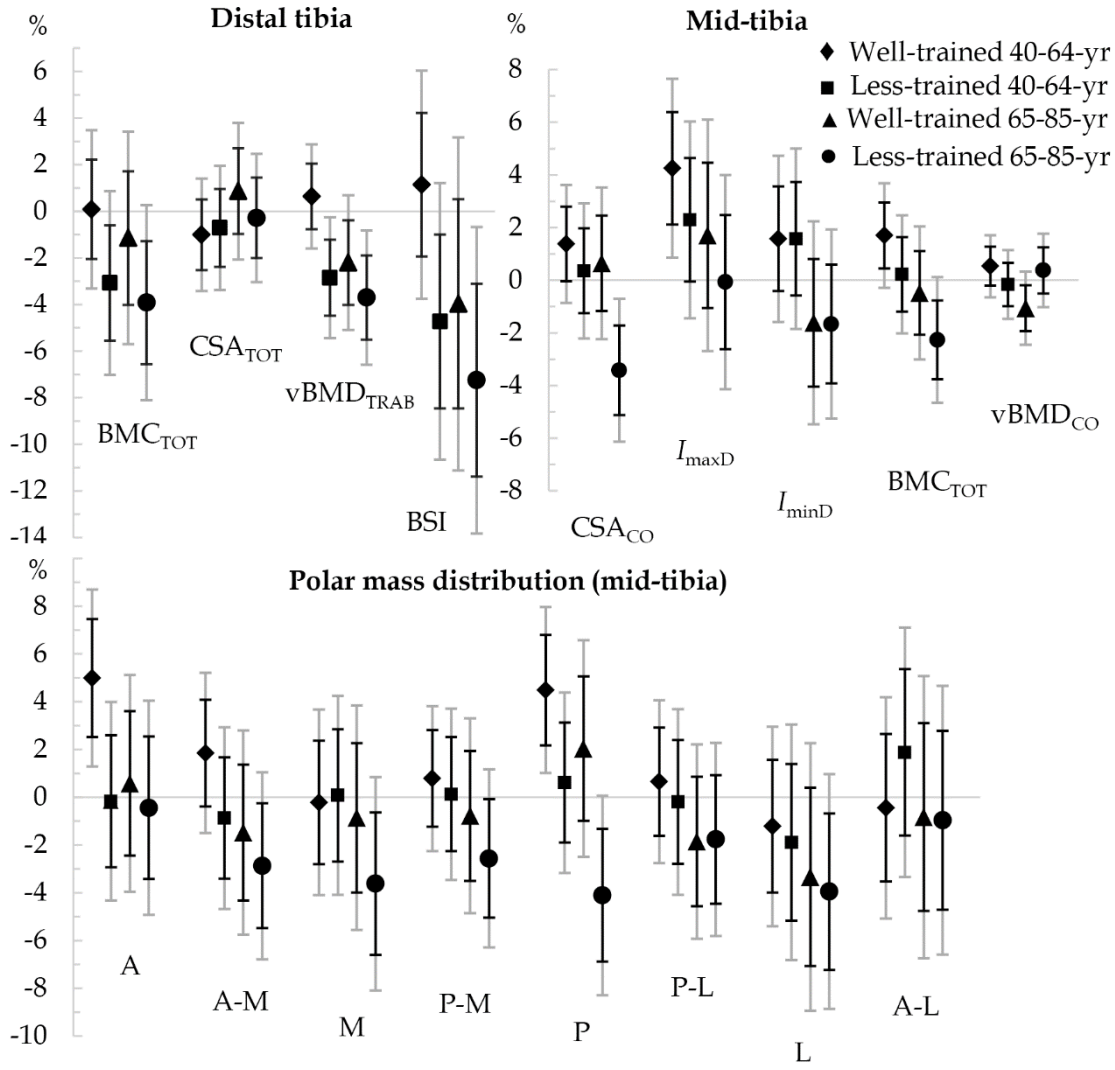

FIGURE 10 10-year percentage changes in distal tibia (*upper left panel*) and tibia midshaft (*upper right panel*) outcomes, and in polar mass distribution of the midshaft (*lower panel*) of the well-trained and less-trained athletes by age group (mean, 95% confidence interval). Black lines show unadjusted confidence intervals and grey lines multiple test corrected confidence intervals. (A = anterior, A-M = anteromedial, M = medial, P-M = posteromedial, P = posterior, P-L = posterolateral, L = lateral, A-L = anterolateral).

5.6 Bone traits after hip fracture (Studies III & IV)

Tables 9 and 10 and Figures 11 and 12 summarize the effects of the home rehabilitation program (Study III) and the associations of physical function and lean body mass with the longitudinal changes in bone in older adults with hip

fracture (Study IV). No differences were observed in baseline bone characteristics between the rehabilitation and control groups.

5.6.1 Effects of the home-based rehabilitation program on tibial bone traits

The 12-month home-based physical rehabilitation program had no effects on the distal tibia or mid-tibial bone traits (Table 9). At the distal site (Table 9, Figure 11), $vBMD_{TOT}$ of the leg on the fractured side, CSA_{TOT} of the leg on the non-fractured side, and BSI of both legs decreased significantly over the 12-month follow-up in both groups. The mean decrease from baseline to 12 months in these bone traits ranged from 0.7% (CSA_{TOT}) to 3.1% (BSI of the non-fractured side). At the mid-tibia site (Table 9, Figure 12), $vBMD_{CO}$ of the leg on the fractured side and CSA_{CO}/CSA_{TOT} and SSI of both legs decreased significantly over the 12-month period in both groups. The mean decrease from baseline to 12 months ranged from 1.1% ($vBMD_{CO}$ on the fractured side, CSA_{CO}/CSA_{TOT} on both sides) to 1.9% (SSI on the non-fractured side).

No significant interaction effects were observed in the women-only analyses, except for CSA_{TOT} of the non-fractured leg and CSA_{CO}/CSA_{TOT} of the fractured leg, which decreased significantly more in the rehabilitation group than in controls (See Paper III for more detail). In the per protocol analysis, no intervention effects were observed (Paper III, Supplementary Tables S1 and S2).

5.6.2 Physical function and lean body mass as predictors of bone deterioration (Study IV)

The associations of physical function and LBM with the changes in tibial bone density and strength at 12 months were examined in Study IV. In the adjusted multivariable regression analyses (Table 10), a lower SPPB score, difficulty in walking outdoors and lower LBM at baseline were associated with a greater decline in distal tibia $vBMD_{TOT}$ in both legs. A lower SPPB score and difficulty in walking outdoors also predicted a greater decline in distal tibia BSI in both legs. At the mid-tibia, a lower SPPB score and lower LBM predicted greater decline in the SSI on the fractured side.

TABLE 9 Distal tibia and tibial midshaft bone traits of the older adults with hip fracture at baseline and at different follow-up points, and p-values for group, time, and interaction effects. Intention-to-treat analysis.

			Distal tibia						Tibial midshaft					
			CSA_{TOT} (mm^2)		$vBMD_{TOT}$ (mg/cm^3)		BSI (g^2/cm^4)		CSA_{CO}/ CSA_{TOT}		$vBMD_{CO}$ (mg/cm^3)		SSI (mm^3)	
Group	Time		Frac	Non	Frac	Non	Frac	Non	Frac	Non	Frac	Non	Frac	Non
Rehabilitation	Baseline		1020 (26)	1046 (26)	225 (8)	227 (8)	0.54 (0.04)	0.56 (0.04)	0.576 (0.015)	0.581 (0.016)	1050 (10)	1057 (12)	1524 (70)	1571 (72)
	3 months		1017 (26)	1037 (27)	222 (8)	226 (8)	0.53 (0.04)	0.55 (0.04)	0.574 (0.016)	0.582 (0.015)	1047 (11)	1053 (12)	1513 (73)	1562 (74)
	6 months		1022 (25)	1036 (25)	221 (8)	224 (8)	0.53 (0.04)	0.54 (0.04)	0.570 (0.016)	0.578 (0.016)	1043 (11)	1051 (12)	1501 (72)	1558 (74)
	12 months		1023 (25)	1039 (25)	221 (8)	224 (8)	0.53 (0.04)	0.54 (0.04)	0.565 (0.016)	0.575 (0.016)	1039 (12)	1049 (12)	1497 (73)	1549 (73)
Control	Baseline		1032 (26)	1033 (25)	207 (8)	209 (8)	0.46 (0.04)	0.47 (0.04)	0.552 (0.015)	0.551 (0.015)	1035 (11)	1032 (11)	1456 (71)	1460 (69)
	3 months		1032 (26)	1035 (26)	205 (8)	207 (8)	0.45 (0.04)	0.47 (0.04)	0.550 (0.016)	0.551 (0.015)	1029 (11)	1030 (12)	1458 (73)	1463 (72)
	6 months		1031 (25)	1030 (24)	204 (8)	208 (8)	0.45 (0.04)	0.47 (0.04)	0.552 (0.016)	0.547 (0.015)	1026 (11)	1030 (12)	1446 (72)	1456 (72)
	12 months		1036 (25)	1022 (24)	204 (8)	207 (8)	0.45 (0.04)	0.46 (0.04)	0.546 (0.016)	0.544 (0.015)	1020 (12)	1027 (12)	1429 (73)	1441 (70)
p-value	Group		0.733	0.718	0.109	0.119	0.131	0.123	0.278	0.165	0.306	0.129	0.500	0.268
	Time	3	0.914	0.718	**0.007**	**0.023**	**0.005**	0.183	0.153	0.883	**0.028**	0.444	0.800	0.679
		6	0.979	0.735	**0.033**	0.083	**0.009**	**0.043**	0.688	0.085	**0.004**	0.475	0.324	0.656
		12	0.541	**0.043**	**0.012**	0.176	**0.016**	**0.018**	**0.025**	**0.001**	**<0.001**	0.099	**0.012**	**0.021**
	Group	3	0.785	0.132	0.714	0.432	0.579	0.312	0.622	0.624	0.531	0.671	0.324	0.318
	× time	6	0.604	0.404	0.424	0.347	0.700	0.076	0.069	0.778	0.829	0.328	0.153	0.496
		12	0.999	0.659	0.553	0.540	0.568	0.567	0.215	0.833	0.482	0.475	0.969	0.864

Values are estimated mean (SE). $vBMD_{TOT}$ = total volumetric BMD, CSA_{TOT} = total cross-sectional area, BSI = compressive bone strength index, $vBMD_{CO}$ = cortical vBMD, CSA_{CO}/CSA_{TOT} = ratio of cortical to total area, SSI = strength-strain index.

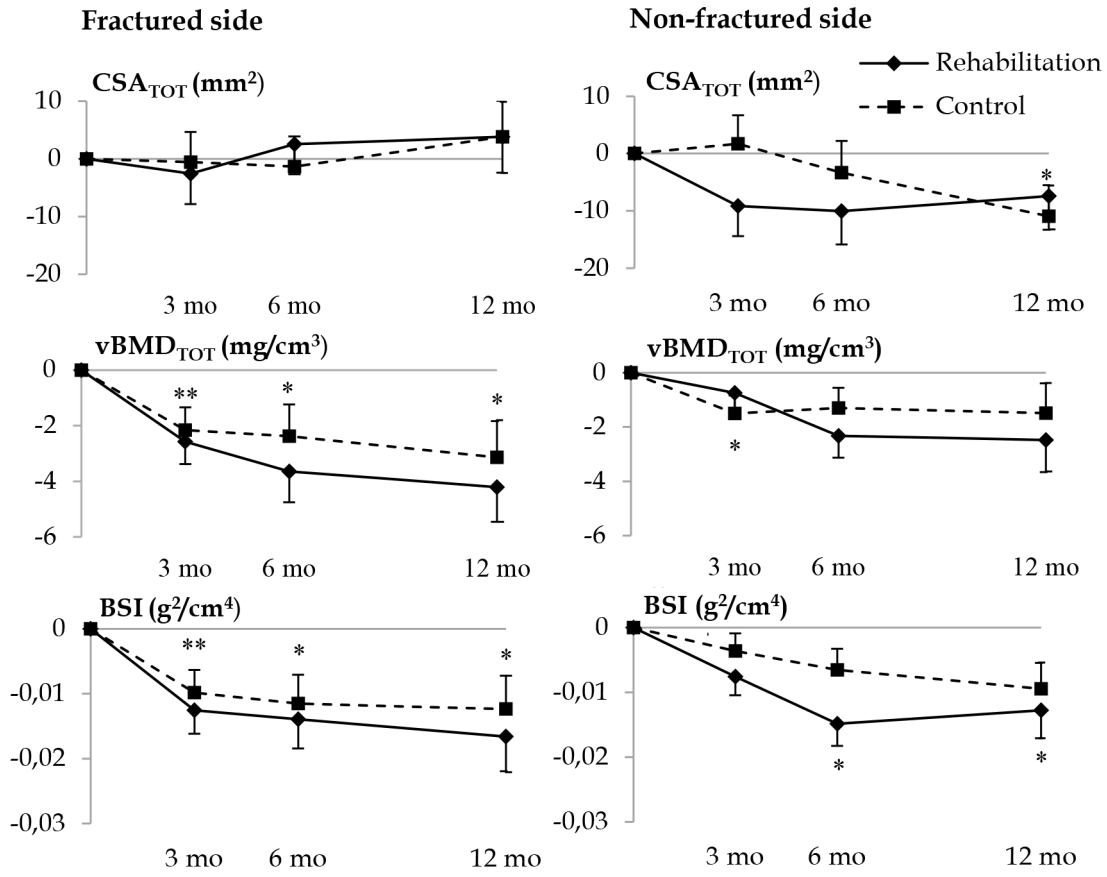

FIGURE 11 Mean change relative to baseline values for distal tibia outcomes of the older adults with hip fracture. Values are (mean, SE) for absolute change. *p<0.05, **p<0.01, ***p<0.001 for the time effect at different time poits.

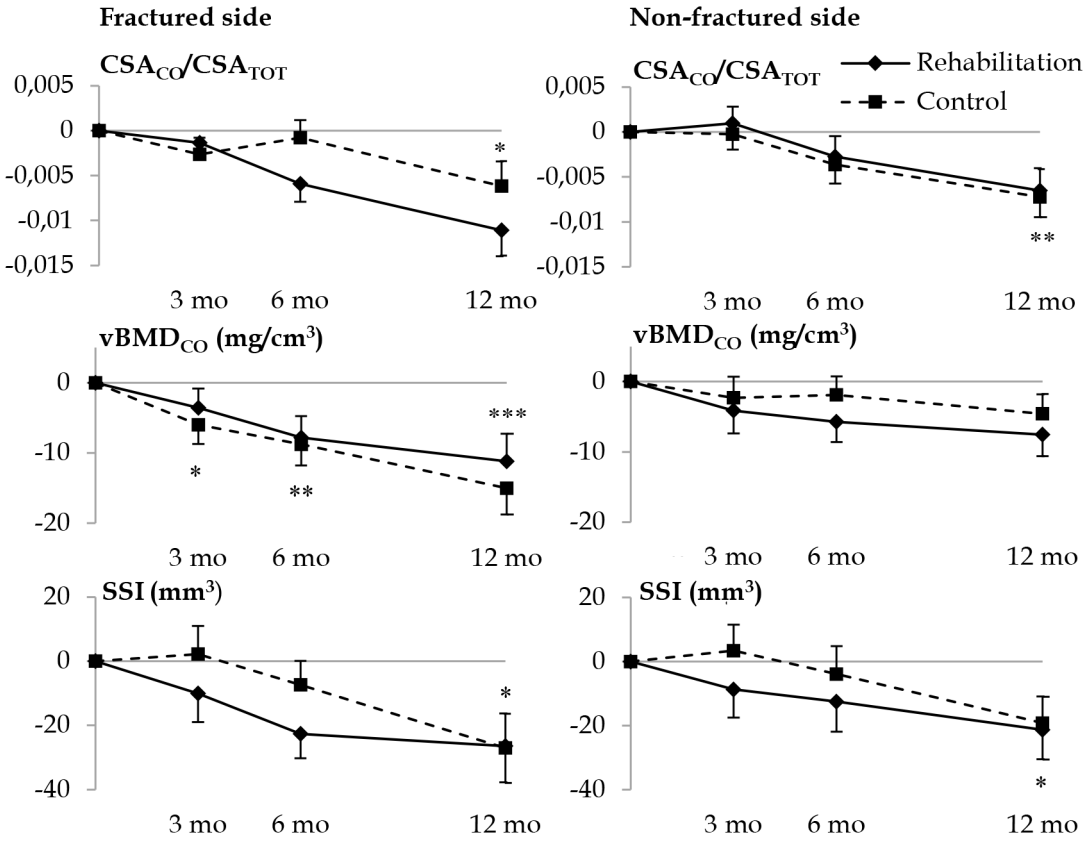

FIGURE 12 Mean change relative to baseline values for tibial midshaft outcomes of the older adults with hip fracture. Values are (mean, SE) for absolute change. *p<0.05, **p<0.01, ***p<0.001 for the time effect at different time points.

TABLE 10 Multiple linear regression models predicting changes in distal tibia and tibial midshaft bone characteristics of the older adults with hip fracture.

	Distal tibia								Tibial midshaft							
	Fractured side				Non-fractured side				Fractured side				Non-fractured side			
	$vBMD_{TOT}$ (n=58)		BSI (n=58)		$vBMD_{TOT}$ (n=59)		BSI (n=56)		$vBMD_{CO}$ (n=57)		SSI (n=58)		$vBMD_{CO}$ (n=58)		SSI (n=57)	
	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	*p*	B (SE)	p	B (SE)	p	B (SE)	p	B (SE)	p
SPPB[a]	-1.44 (0.64)	**.028**	-3.09 (1.33)	**.023**	-1.34 (0.64)	**.040**	-3.06 (1.11)	**.007**	-.538 (0.46)	.247	-2.03 (0.93)	**.034**	-.193 (0.43)	.655	-.062 (0.78)	.938
Walking outdoors[b]	-2.05 (0.74)	**.009**	-3.62 (1.53)	**.024**	-2.67 (0.74)	**<.001**	-5.69 (1.28)	**<.001**	-.371 (0.54)	.485	-0.60 (1.08)	.578	-.356 (0.50)	.476	-.343 (0.90)	.711
Lean body mass	.152 (0.06)	**.010**	.136 (0.12)	.258	.151 (0.06)	**.010**	.152 (0.10)	.126	-.025 (0.04)	.531	.171 (0.08)	**.042**	-.004 (0.04)	.910	.129 (0.07)	.067
	R^2=.236	<.001	R^2=.182	.006	R^2=.363	<.001	R^2=.428	<.001	R^2=.119	.286	R^2=.247	.023	R^2=.015	.566	R^2=.157	.421

The models were adjusted for age, sex, surgical procedure, number of chronic diseases and use of bisphosphonates at baseline. Sample size reduction due to weighting ranged from 5 to 10%. $vBMD_{TOT}$ = total volumetric bone mineral density, BSI = compressive bone strength index, $vBMD_{CO}$ = cortical vBMD, SSI = strength-strain index, SPPB = Short Physical Performance Battery; [a] 0) high performance (score ≥7), 1) low performance (score <7); [b] 0) without difficulties/minor difficulty, 1) major difficulty/unable.

6 DISCUSSION

This study investigated the adaptive responses of aging bone to physical exercise in older adults situated at the two poles of the physical activity, physical performance, and bone health spectrums: at one end middle-aged and older male masters athletes with a life-long physical training history and at the other end older men and women who had sustained a recent hip fracture. The 20-week high-intensity strength and sprint training program designed for the athletes induced significant, albeit modest improvements in mid-tibia cross-sectional geometry and strength. Long-term effects of continued intensive training were manifested as maintained distal tibia bone mass, density and strength, and maintained or even improved mid-tibia bone mass and cross-sectional geometry over the 10-year follow-up period. Conversely, the yearlong home exercise program on mobility recovery designed for the hip fracture sample was unable to counteract bone weakening after the hip fracture. The distal and mid-tibial bone cross-sectional geometry, density and strength of the patients with hip fracture continued to weaken during the year following the fracture, in both the leg on the fractured side and the contralateral leg. At the distal tibia site, lower physical function and lower LBM predicted greater post-hip fracture deterioration in bone traits.

6.1 Adaptive responses of aging bone to exercise and contribution to age-related bone loss

In the present study, high-intensity strength and sprint training had positive effects on the athletes' tibial bone properties, both following the 20-week intervention and over the 10-year follow-up period. Only a few studies have demonstrated geometrical adaptation of aged bone, and no previous trials exist on aging athletes. Longitudinal studies on the effects of high-intensity exercise on age-related bone deterioration are also few. Furthermore, the effects of exercise on bone geometry and strength among older people with low physical

function and reduced bone mass have not been extensively studied, and no previous longitudinal studies have been published on patients with hip fracture. Moreover, this was the first study on such patients to examine the effects of exercise on the bone properties of the leg on the fractured side. This was considered to merit investigation as the effects on the leg on the fractured side may differ from those on the contralateral leg, owing, for example, to disuse. The present home rehabilitation program was, however, unable to induce osteogenic effects in either leg. The results accord with the very few existing trials on the effects of physical exercise on bone after hip fracture that have found no effects on aBMD of the contralateral hip either following a yearlong home-rehabilitation program (Orwig et al. 2011) or a more resistive six month´s training program (Binder et al. 2004). Similarly, previous results on older people comparable to patients with hip fracture have also shown minor or no effects on aBMD (Papaioannou et al. 2003; Villareal et al. 2004; Korpelainen et al. 2006).

The present study examined osteogenic adaptations at two different, weight-bearing bone sites comprising different bone tissue types and different loading environments. The distal tibia mainly comprises trabecular bone and is subjected to axial compression from impact loading (ground reaction forces). In sedentary older people, 12-months' impact training increased distal tibia bone mass and estimated strength (Uusi-Rasi et al. 2003). Similarly, both eight months' high-intensity resistance training and machine-based isometric axial compression exercise maintained distal tibia BSI in middle-aged and older men with osteopenia or osteoporosis as compared with men who continued habitual physical activity (Harding et al. 2020). In the present study, no intervention effects were observed at the distal site following either the home rehabilitation program or the high-intensity strength and sprint training program. The absence of osteogenic effects probably relates to the physical functioning and initial bone values of the participants as well as to the mode, intensity, and duration of the training programs used. The ProMo program was designed to restore mobility, and bone outcomes were only a secondary consideration. Despite being progressive and including elements of the multicomponent programs optimal for preserving bone health during aging (such as weight-bearing strengthening exercises, agility, and balance training), the intensity of the program was probably too low for osteogenic adaptation, and there was no major impact element. Furthermore, most of the ProMo participants were using rollators, which may have further reduced the impacts sustained during walking and other weight-bearing activities. In young adults, use of a rollator affects walking biomechanics by, for example, reducing ground reaction forces (Youdas et al. 2005) and unloading the quadriceps muscles (Alkjær et al. 2006). Despite the limited data on older adults (Mundt et al. 2019), highlighting the importance of the correct walking technique (proper heel impact) may be advisable for rollator users.

The 20-week program used in the Athlas study included progressive and versatile high-impact training comprising sport-specific sprint training and diverse plyometric exercises. Despite this, no changes were observed at the distal

tibia site. A possible explanation is the long-term impact training history of the athletes (lack of novelty in the training stimulus) and the short duration of the training program for densitometric adaptation. At the 10-year follow-up, in accordance with previous cross-sectional (Ma et al. 2009; Wilks et al. 2009a) and experimental findings (Uusi-Rasi et al. 2003; Harding et al. 2020), distal tibia bone mass, compressive strength and trabecular vBMD, in particular, were found to have been maintained in the participants who had continued regular strength and sprint training and to have declined in those who had reduced their training load. Similar changes were observed in a 4-year longitudinal study (Ireland et al. 2020) in which sprint-trained older athletes showed better maintenance of distal tibia compressive strength than endurance-trained counterparts. In line with our findings, the differences were explained by better maintenance of trabecular BMD without changes in CSA, a reasonable result given the relative stability of the total area in the distal tibia site.

The mid-tibia comprises cortical bone and is subjected to diverse bending and torsional loads from muscular contractions and ground reaction forces. In ProMo, no effects were observed in mid-tibia geometry, density, or strength. In the Athlas study, in accordance with previous cross-sectional athlete (Liu et al. 2003; Rantalainen et al. 2010; Korhonen et al. 2012) and twin (Ma et al. 2009) studies, the adaptations in cortical bone at the tibial shaft site were mostly structural and no changes occurred in bone/cortical density. The structural improvements were observed both following the 20-week intervention and over the 10-year follow-up period. The present findings accord with previous research in older men showing that a lifetime history of weight-bearing sport and leisure activities improved cortical bone strength at the loaded sites through an increase in bone mass and size, but had no effect on cortical BMD (Daly & Bass 2006). In Athlas, the lack of training-induced improvements in $vBMD_{CO}$ could be related to the normal or high pretraining BMD values of the participants, a phenomenon also observed in some previous studies (Nichols et al. 1995; Pruitt, Taaffe & Marcus 1995; Vincent & Braith 2002; Ashe et al. 2013; Bolam, van Uffelen & Taaffe 2013). Another possible reason for the absence of change in vBMD is the short duration of our intervention. Changes in bone geometry occur relatively quickly, whereas it may take several months or even years to complete secondary mineralization (Martin & Seeman 2008). In the Athlas RCT, bone mineralization might have occurred later. Due to earlier growth in bone size, bone density may temporarily decrease, as observed in the present per protocol analysis and also previously in adolescents (Bass et al. 1999). A decrease in cortical density may also reflect exercise-induced targeted remodeling and the resulting intracortical porosity (Hughes et al. 2020), as also suggested by previous cross-sectional studies (Wilks et al. 2009a; Rantalainen et al. 2011). In the 10-year follow-up, the age-related changes in cortical density were manifested as maintained $vBMD_{CO}$ in both the well-trained and less-trained athletes. Contrary to Ireland et al. (2020), whose results indicated better maintenance of cortical vBMD in sprint than endurance trained older athletes, no significant group differences were observed in this study. Many of the present less-trained athletes were still competing in

sprint events, and while their training might have been adequate for preserving cortical density, it was insufficient to maintain the geometrical properties.

In line with previous cross-sectional findings (Ma et al. 2009; Wilks et al. 2009a; Rantalainen et al. 2010; Korhonen et al. 2012), the greatest changes in bone geometry following the 20-week intervention were observed in mid-tibial cortical thickness. In addition, there was a tendency towards increased cortical CSA in the experimental group. In the per protocol analysis, the increase in cortical CSA as well as in total BMC was significant. Previous intervention studies on premenopausal (Vainionpaa et al. 2007) and postmenopausal women (Adami et al. 1999; Uusi-Rasi et al. 2003; Karinkanta et al. 2007) have found parallel results (Adami et al. 1999; Uusi-Rasi et al. 2003; Karinkanta et al. 2007; Vainionpaa et al. 2007), whereas other studies on older women (Ashe et al. 2013) and men (Kukuljan et al. 2011) have found no effects on mid-tibial or mid-femoral structure, strength or vBMD after up to 18 months' strength and/or impact training. Comparisons with previous research are, however, limited to differences in study populations, training programs, intervention duration and the bone sites measured. The present exercise-induced increases in mid-tibia BMC and CSA_{CO} were also observed in the 10-year follow-up. In line with previous longitudinal findings on masters athletes (Ireland et al. 2020), BMC and CSA_{CO} increased in the well-trained athletes while they decreased in the less trained group over the 10-year period. After adjusting for multiple testing, the group differences in these parameters were no longer significant, although a trend towards increased cortical area remained in the well-trained compared to less-trained athletes.

The improved mid-tibial structural properties were located by the mass distribution analyses. According to the per protocol analysis of the Athlas RCT, the increase in bone mass occurred in the A-M region while in the 10-year follow-up study, the bone mass of the well-trained athletes increased in the A-P direction. A site-specific increase in bone mass in the A-P direction has also been observed in previous cross-sectional athlete (Bailey, Kukuljan & Daly 2010; Rantalainen et al. 2010; Korhonen et al. 2012; Weatherholt & Warden 2016) and twin studies (Ma et al. 2009), and in a 12-month RCT combining hormone replacement therapy with high-impact training (Cheng et al. 2002). In those studies, the adaptation was manifested as increased bending strength along the maximum axis, a site which reflects the habitual loading pattern in weight-bearing activities (Yang et al. 2014). In the present RCT, bone mineral mass increased in the A-M region, and the intervention-related increase in bending resistance was observed largely along the minimum axis (I_{min}). Instead of the habitual loading pattern of sprint training (I_{max}), the adaptation probably occurred in response to diverse bending strains from increased and intensified plyometric and strength training, the latter being a particularly novel stimulus for the athletes. In the present 10-year study, as also reported by Ireland et al. (2020), I_{max} increased in both groups, although the well-trained athletes showed an increasing trend. The observed increase in I_{max} may also reflect age-related endocortical resorption and compensatory periosteal apposition.

In community dwelling middle-aged and older men, long-term participation in diverse weight-bearing recreational and sporting activities has been associated with skeletal adaptation in both the A-P and M-L planes and along both the I_{max} and I_{min} axes (Bailey, Kukuljan & Daly 2010). In the Athlas RCT, the increased bone mass in the A-M region indicates that the increase in bending strength did not occur unambiguously in the direction of the greatest or the smallest flexural rigidity, but in the A-P direction between the maximal and minimal moments. The increase in bending strength was more pronounced in the per protocol analysis, in which cortical vBMD decreased. The increase in cortical thickness and in the area without significant external expansion (data not shown), and the accompanying decrease in cortical vBMD may indicate corticalization of the subcortical trabecular bone, a phenomenon that has also been observed in premenopausal women (Heinonen et al. 2012). In the 10-year follow-up, the exercise-induced adaptations were also more likely to occur in the endocortical than periosteal surfaces, as again no significant external expansion was found (data not shown). These observations support findings on animals (Birkhold et al. 2016) suggesting that, during aging, mechanoresponsiveness is better preserved on the endocortical surface than on the periosteal surface.

In the Athlas RCT, the high initial bone values and the rather short training period did not prevent adaptation of the mid-tibia structural traits. As also concluded in a meta-analysis by Souza et al. (2020), with sufficient training stimulus and in those with better initial values, adaptation may occur faster. The Athlas RCT was one of the first studies to apply principles followed in the training of young athletes to middle-aged and older adults, and the intensity of the exercises was high. In order to produce osteogenic effects, the exercises to be performed should be aligned with the appropriate mechanical loading characteristics (strain environment) and follow the principles of specificity, overload, reversibility, initial values, and diminished returns (Kohrt et al. 2004). In Athlas, loading characteristics, specificity and overload were carefully considered when designing the program, and hence the high-impact exercises were combined with heavy and explosive strength exercises targeting the lower legs. With respect to the strain environment (Lanyon 1996; Hart et al. 2017), the exercises were likely to induce high-magnitude strains that were rapid, unusual in their distribution, short in duration and relatively low in repetition. In light of the mechanostat theory (Frost 1987), the novel, intensified training program likely induced a strain stimulus greater than the customary level, and hence a state of overload, at least at the mid-tibia where localized structural adaptation was observed. At the distal tibia, on the contrary, lack of novelty in the strain stimulus may have limited adaptation despite possible high levels in some components of the strain stimulus. With respect to the other training principles, the program was progressive and periodized in order to maintain novelty and overload, and to minimize overtraining and injuries. Attention was also paid to the correct exercise techniques. Under these somewhat optimal loading characteristics, changes in bone geometry and strength were observed in the participants already engaged in high-impact exercise. Four training sessions per

week with variation in intensity and type of work appeared to provide overload with no indication of overtraining or of the stress fractures that can result from excessive repetitive loads in the absence of appropriate recovery.

In ProMo, the lack of exercise-induced changes in the mid-tibia could again be explained by the intensity and specificity of the independently performed program as well as by the fragility of the participants. The strengthening exercises for the lower legs were performed using resistance bands, and it is likely that the bending and torsional loads were insufficient for mid-tibial adaptation. Although the relative intensities of the exercises (both strengthening and agility) may have been high, at least initially and especially for the frailest participants, the absolute intensities were probably low. Both the ground reaction and the muscle contraction forces were likely to have been low, resulting in an overall strain stimulus that did not exceed the thresholds for overload or maintenance (Frost 1987). Although the loading-induced strains may have been novel and diverse, the key components of the strain stimulus, i.e., magnitude (Rubin & Lanyon 1985) and the rate (LaMothe, Hamilton & Zernicke 2005), were likely to have been low, further contributing to an overall stimulus insufficient for bone adaptation. To produce higher impacts, training programs for osteoporotic participants unaccustomed to impact training might more fruitfully begin with progressive strength training, as this would build strength for impact training. Thereafter, the participants could progress from performing low to moderate or high-impact exercises (Taaffe et al. 2013; Cauley & Giangregorio 2020). However, for the frailest patients with hip fracture, a program of this kind might not be advisable. In those with reduced bone mass, even low intensity resistance training may be effective in reducing bone loss (Souza et al. 2020), although, at least for healthy aging people, high-intensity exercise seems to be a more effective training stimulus than exercise of moderate or low-intensity (Kistler-Fischbacher, Weeks & Beck 2021a; Kistler-Fischbacher, Weeks & Beck 2021b). In ProMo, the rehabilitation program increased physical activity (Turunen et al. 2017), improved mobility recovery (Salpakoski et al. 2014) and was feasible in the home setting. Despite this and the suggested benefits of even low intensity exercise (Souza et al. 2020), bone properties at both tibial sites continued to weaken during the year following the fracture. These results, when combined with those observed in the Athlas study, support the suggestion that in older people, the thresholds for bone maintenance and overload may be higher (Guadalupe-Grau et al. 2009; Meakin et al. 2014; Cauley & Giangregorio 2020) and that a high strain magnitude and/or rate and an unusual distribution may become even more important (Javaheri & Pitsillides 2019; Kistler-Fischbacher, Weeks & Beck 2021a), owing, for example, to dampened mechanosensitivity (Hemmatian et al. 2017).

6.2 Post-hip fracture bone loss and associations with physical function and lean body mass

Post-hip fracture bone loss in the present study was manifested as decreased distal and mid-tibial cross-sectional geometry, volumetric density and estimated strength during the year after the fracture. Depending on the bone variable, the mean decrease from baseline to 12 months ranged from 1 to 3%. Owing to the time frame between the fracture and the baseline measurements (approximately 10 weeks), the true annual decrements following the fracture were probably even larger, as the greatest bone loss, at least for BMD, is likely to occur during the first 2-3 months post fracture (Fox et al. 2000; Magaziner et al. 2006). In the distal tibia, a significant decline in the compressive strength index was observed in both legs during the year after the fracture. In the fractured leg, the decline was explained by a decrease in total density, whereas in the non-fractured leg, bone loss was also evident in total area. The changes in CSA_{TOT} were however small (<1%/year) and probably did not exceed the precision error of the pQCT measurements for the structural and strength parameters in participants with fragile bone structures. At the mid-tibia site, bone deterioration in the non-fractured leg was manifested as a decrease in SSI and the ratio of cortical to total area, whereas on the fractured side, bone loss was also evident in cortical vBMD. Based on the evidence on both age-related (Zebaze et al. 2010) and disuse-related (Hughes et al. 2020) bone loss, this could reflect greater intra-cortical bone loss and the resulting intra-cortical porosity in the fractured than non-fractured leg. In addition to bone density, the overall bone deterioration at both bone sites was more pronounced in the fractured leg, which could, at least in part, be explained by disuse, as also suggested in the cross-sectional study by Mikkola et al. (2007).

As the rehabilitation intervention had no effect on bone, we combined the data of the study groups, and examined the potential predictors of the loss in bone density and strength. Only a few studies have examined the predictors of post-hip fracture bone loss (Wehren et al. 2004; 2005) and none of these have studied the actual changes in bone over time, or included results for the leg on the fractured side. In the present study, the specific interest was in the contribution of physical function and lean body mass to bone deterioration during the post-fracture year. With respect to physical function, we observed that a SPPB score under 7, which indicates high risk for disability (Guralnik et al. 1995) and major perceived difficulty in walking outdoors predicted a greater decline in distal tibia vBMD and compressive strength in both legs. Lower LBM, on the other hand, was associated with a greater decline in vBMD in both legs. Despite more pronounced bone deterioration in the leg on the fractured side, no between-side differences in the predictors were found, except for mid-tibia SSI. At the mid-tibia site, a lower SPPB score and lower LBM predicted a greater decline in bone strength, but only on the fractured side. Neither of the studied factors, however, predicted the decline in SSI on the non-fractured side nor the decline in cortical vBMD on either side, suggesting that the mid-tibia may not be equally sensitive

to differences in the predictors used. The loading environments of the different bone sites are also different, and the thresholds for bone adaptation (disuse, maintenance, overload) are also likely to differ according to the typical strain level of the bone site in question (Hsieh et al. 2001). In previous studies on older men and women, muscle force, and especially muscle power (Ashe et al. 2008; Cousins et al. 2010; Chalhoub et al. 2018), has been associated with mid-tibial bone strength. In the present study, however, leg strength and power did not correlate with the bone changes (data not shown), probably owing to the fragility and heterogeneity of the study population and the amount of missing data. Low physical function and pain may have also influenced on the performing of maximal efforts.

The associations of physical function with bone deterioration found in this study accord with previous findings indicating better functional recovery in patients with better function (Sipilä et al. 2011) and support the hypothesis of better bone recovery in patients with a better capacity to load their bones. Among older people, walking outdoors has also been associated with a greater amount of objectively measured physical activity (Portegijs et al. 2015), and hence possibly also with increased bone loading. Furthermore, our results support those of previous studies suggesting better post-fracture functional recovery (Di Monaco et al. 2007) and reduced age-related bone loss (Kim et al. 2018) for men with higher LBM. Owing to the strong relationship between bone and muscle, changes in muscle could be reflected in changes in bone. Moreover, in older, often frail and undernourished, patients with hip fracture, higher lean body mass may also reflect better resources to cope with a prolonged catabolic state and hip fracture-related stresses. In the present study, however, the LBM values were, rather high owing to the inclusion criteria (home-dwelling, ambulatory).

6.3 Factors contributing to bone loss and adaptation to increased loading

Several factors such as age, sex, initial bone values, muscle strength, hormonal and nutritional factors, medications, and diseases may contribute to bone adaptations to increased or decreased loading in old age. The effects of these factors were not specifically examined in the present study, but their potential contribution should be considered when interpreting the results. In Athlas, with the exception of participant age, the study sample was rather homogeneous whereas in ProMo, considerable heterogeneity in participant age, physical functional capacity and bone properties increased the individual variability in the bone results. In ProMo, the number of patients with the greatest difficulties in walking outdoors was higher in the rehabilitation group compared to controls, although no significant between-group differences were found. In our previous subgroup analysis (Sipilä et al. 2016), intervention-induced mobility gains were observed only in the patients with better physical functional capacity, leading us

to speculate that the program was too demanding for those with severe mobility difficulty. This consideration may also have affected the results of the present study, although the lack of specificity and intensity of the training seems more a plausible reason for the lack of osteogenic effects. Furthermore, it is well known that initial bone values may contribute to bone adaptations not only to increased but also decreased loading. The initial bone loss may be greater in those with the highest initial values (reflecting regression to the mean), a phenomenon that has also been observed following a hip fracture (Wehren et al. 2004). In the present study, this phenomenon was not indicated among either athletes or people with hip fracture. In ProMo, due to the timeline between the fracture and the baseline measurements, the greatest initial bone loss and the possible regression to the mean might have already happened.

In Athlas, especially, the age range of the participants was wide. Owing to possible age-related differences in the athletes' current and previous training habits, intervention-related training, and bone adaptability, separate age group analyses for the 40- to 64-year-olds and 65- to 85-year-olds were conducted in both the intervention study and follow-up study. In both studies, the structural changes at the mid-tibia site were more pronounced in the older age group. The overall intervention-induced increase in the amount and quality of training might have been greater in the older age group, in which the amount of previous strength training was lower. The 10-year results, on the other hand, indicate that the bending strains imposed by strength and plyometric training may be an efficient way to preserve bone structure even in old age.

Unlike the structural changes at the mid-tibia site, the densitometric changes over the 10-year follow-up were more pronounced in the 40- to 64-year-old group. This may be explained by the higher vertical compression forces exerted during the impact-type training. It is well known that normal aging processes limit training tolerance (e.g., reduced recovery) and that many masters competitors cannot maintain their absolute training intensity and volume after entering old age (Foster et al. 2007; Tanaka & Seals 2008; Fell & Williams 2010; Harridge & Lazarus 2017; Lazarus & Harridge 2017). Even in the well-trained group, absolute training intensities were likely to be lower in the older than younger athletes, even if both age groups had a similar relative training load. This probably also holds true for the intervention. The younger group was probably able to train harder than the older group, as shown, in particular, by the intensity of their intervention-related strength training, which was very high. Following the 20-week intervention, mid-tibia bending strength increased in the 40- to 64-year-olds but not in the 65- to 85-year-olds. Overall, older age did not prevent adaptation in either of the athlete studies, as changes were observed in both age groups.

In ProMo, 80% of the participants were women whereas in Athlas, all the participants were men. Although osteoporosis is much more common in females, a strength of this study is that it addressed an important knowledge gap on the osteogenic effects of exercise in middle-aged and older men. At the same time, sex differences limit the comparability of the bone results (adaptation and

maintenance) for the two study samples located at the two poles of the spectrums of interest in this dissertation. In addition to sex differences in bone characteristics and bone aging, differences in muscle mass and strength between the sexes should also be noted with respect to their potential impact on bones through multiple mechanical and non-mechanical muscle-bone relationships (Laurent et al. 2016; Kirk et al. 2020). The fact that ProMo included both sexes, further increased the variability in the results. The changes in bone density and structure after a hip fracture may in part differ between the sexes (Rathbun et al. 2016a; Rathbun et al. 2016b), as also may osteogenic responses to increased loading. It has been suggested that osteogenic adaptation to physical exercise is greater in men, owing, for example, to reduced mechanosensitivity caused by age- and menopause-related estrogen deficiency (Guadalupe-Grau et al. 2009). However, older men have been less studied, and more research is needed to confirm whether sexual dimorphism exists in bone response to exercise. Moreover, sport and exercise studies have more often utilized men while research on osteoporosis has focused on women, which may also confound comparisons between the sexes. In ProMo, the low number of male participants did not allow separate analyses for both men and women or comparisons between the sexes. The results of the analyses restricted solely to women did not differ from the main analysis (see Paper III for more details).

Participant characteristics related to hormones, medication, and dietary factors are shown in the individual publications. No between-group differences were observed in these factors in any of the studies. There were no evidence of vitamin D deficiency in the Athlas participants. In the ProMo participants, the mean levels of serum 25OHD were slightly above the minimum level of 50 nmol/l (Holick 2007), although lower than is generally recommended for bone health (75 nmol/l). In Athlas, the athletes' testosterone values were normal, and the changes in bone variables during the 20-week intervention were not related to the changes in total T levels (data not shown). Moreover, the testosterone values of the older age group did not differ from those of the younger age group, and therefore were unlikely to account for the observed differences in training responses between the two age groups. The athletes were free of medications affecting bones whereas one-third of the ProMo participants were using bisphosphonates, a medication which may have limited the bone cell response to exercise (blunted bone turnover).

In ProMo, we observed multimorbidity, which is typical among older people with hip fracture. However, the number of chronic diseases was taken into account in the regression analyses. Nevertheless, owing to our inclusion criteria, the participants were probably healthier than patients with hip fracture on average. Masters athletes, in turn, tend to be heathier than their average age peers (Kettunen et al. 2006). Although the athletes in the present study were screened for their health status, they were not universally healthy, and chronic diseases were present not only in the experimental and control group participants but also among the well-trained and less-trained athletes. Therefore, the possible effect of diseases cannot be totally excluded. The athletes with

diseases did not, however, differ from the healthy athletes in their physical performance, body composition, training response, age-related bone changes, or testosterone levels, indicating the presence of a therapeutic equilibrium and that the diseases had no effect on the results.

On the question of diseases, the effect of genes on the present results cannot be totally excluded. Genes contribute to individual training responses and exercise behavior (Bouchard, Rankinen & Timmons 2011) and could also affect the ability to maintain intensive training into old age. Bone properties are strongly determined by genes (Mikkola et al. 2008; Wagner et al. 2013), and age-related bone loss probably also has a genetic component (Ralston & de Crombrugghe 2006; Mitchell & Yerges-Armstrong 2011). However, the heritability of the bone properties studied appear to be higher in younger compared to older populations, in which higher individual variation in bone properties is probably attributable to age-related variation in environmental factors (Mitchell & Yerges-Armstrong 2011). The influence of environmental factors appears to be considerable, especially in the load-bearing lower limbs (Mikkola et al. 2008).

6.4 Methodological considerations

The strengths of this study include the use of randomized controlled study designs and of longitudinal follow-up designs of sufficient length to detect changes in bone. In Study I, the intervention was relatively short (20 weeks) and independently performed. This may, in part, explain the relatively modest changes in bone structure and strength and the lack of increase in bone density. The main limitation in Studies III and IV is that they report the secondary outcomes of an RCT. The ProMo intervention targeted mobility recovery. Owing to missing bone data, it was likely underpowered to detect adaptations in bone. Moreover, the lack of specificity of the training program limits the ability to draw conclusions on the adaptive capacity of a fragile bone to increased loading. Furthermore, Studies II and IV are limited to associations only, not causal relationships. In Athlas, the RCT and the 10-year follow-up were designed and executed by the same study group, which enhances the comparability of the short-term and long-term results. The strength of Study IV lies in its prospective nature.

In ProMo, we had a population-based clinical study sample. However, the participants were community-living, and the results may not be generalizable to all older adults with hip fracture. The present studies were part of larger research programs that included RCT designs, and hence the study samples were also carefully selected in the longitudinal follow-up studies to represent both home-dwelling older adults with hip fracture and highly trained, competitive athletes. The athletes were highly motivated and able to participate in vigorous training of a kind which could affect their bones. Therefore, the target intensities of the training intervention were likely to be achieved. In Athlas, we had an active

control group, whose members may have increased or intensified their training. Together with the similarity of the training practices of the experimental control groups, this could also explain the modest changes observed. In Study II, the group allocation to well-trained and less-trained athletes was based on self-reported physical activity levels. However, with an athlete population accustomed to keeping training diaries on a regular basis, the probability of recall bias is likely to be lower than average. In ProMo, although the study sample was representative of home-dwelling older adults with hip fracture, heterogeneity in age, physical function, and especially sex, increased the variability in the bone results. This, together with the lack of specificity of the training program, restricted the conclusions that could be drawn on the adaptability and maintenance of bone, and on the factors associated with the changes in bone. Moreover, in ProMo, the information on the past physical activity of the participants only covered the year preceding the fracture, which also limits the ability to contrast their results with those of athletes with a lifetime history of physical activity.

In Athlas, given the highly intensive, independently performed training program, intervention adherence was high. In ProMo, compliance with the independently performed home exercises was moderate and comparable to that reported in similar studies elsewhere (Latham et al. 2014; Pahor et al. 2014). Compliance with the physical activity counseling in ProMo was, however, excellent. Dropouts were few in both interventions. The interventions were well tolerated, and no intervention-related adverse effects were reported in either of the studies. Given the long-term follow-up, the retention rate in the 10-year follow-up study of the athletes was also relatively high.

The current studies have multiple outcomes. In Study I, the power calculations were made to allow multiple primary outcomes. In Study II, the results are presented both in raw form and as corrected for multiple testing. The findings on age group comparisons should, however, be interpreted with caution, as the sample size calculations were not made with this in mind. Hence, the age group analyses are exploratory only, i.e., hypothesis-generating rather than hypothesis-confirming. Studies III and IV, in turn, report secondary outcomes of an RCT, and the sample size calculations were made on mobility recovery. Overall, the sample sizes in the present studies, especially in the restricted analyses, were relatively small, although comparable to several other exercise interventions and follow-up studies. Additional analyses were included, and, in order to describe the mechanisms behind the bone changes, multiple outcomes were preferred over a single outcome.

Different statistical methods were used in different studies to examine the effects/associations of training on/with the bone changes. In Study I, we used a standard repeated analysis of variance methodology. The method was chosen as the study design was rather simple: we had only two time points and missing data were minimal. In the 10-year follow-up (Study II), we used linear mixed models, which are more flexible and generally preferred over RM-ANOVA nowadays. In ProMo, contrary to Athlas, we had multiple time points and the

amount of missing data was considerable, partly because of the frailty of the study population. In Study III, we were able to account for this by using a specifically tailored maximum likelihood estimation method. The effect of the intervention was assessed by GLM for longitudinal data. The models were adjusted for age as, unlike in the Athlas RCT, randomization was not stratified by age. In both RCTs, additional analyses were performed by adjusting the models for different covariates such as sex, body weight and testosterone levels, but these were not reported in the papers as the results were not different from those of the main analyses. In Study IV, which examined the predictors of bone loss, a robust linear regression approach was used to down-weight the influence of extreme outliers. While this further reduced the already small sample size, it yielded more reliable regression coefficients. Because of the sample size and the amount of missing data, we had to limit the number of possible confounders included in the analyses.

A clear strength of this study was the use of pQCT imaging to examine changes in bone cross-sectional geometry and volumetric density. pQCT, which was used in all the studies, is precise and reproducible. A further strength of pQCT is that it enables detailed bone mass distribution analyses, only relatively few of which have been performed earlier. Furthermore, we were able to measure two different types of bone site containing different bone tissue types. The tibia is not, however, a site of osteoporotic fracture during aging, and hence the inclusion of measures of the proximal femur and/or spine would have added value to our study and, at least for ProMo, enhanced its comparability to previous studies. DXA would have also provided more accurate lean body mass results. Furthermore, the constraints related to pQCT should be kept in mind when interpreting the results. However, in Athlas, at least at the mid-tibia site, where the cortices are thick, partial volume effect should not be an issue. Beam hardening may have had some impact on our results, but probably not on the effect of the intervention. Most importantly, a higher scan resolution would have provided more detailed results on, for example cortical porosity or trabecular architecture. Scan resolution also limits the utility of the pQCT-derived muscle outcomes, which were not, therefore, considered in this study. Muscle cross-sectional area, for example, could be used to assess site-specific association between muscle and bone. However, based on previous studies (e.g., Rantalainen et al. 2013), the tibia is more likely to be loaded with muscle pull from the knee extensors than from muscles located at the tibial site. Hence, the calf muscles may not adequately reflect the differences in the effects of training on the tibia. Finally, we used different image analysis methods in the different study programs, and hence the bone values of the athletes and patients with hip fracture are not fully comparable. However, the same methods were used at the baseline and follow-up measurements in these projects. Owing to the low cortical density and extremely thin cortices of the older adults with hip fracture, a threshold-free analysis method was preferred over traditional density-based segmentation. Overall, as compared with a traditional density-based method, the OBS method tends to give slightly higher values for cortical area and lower values for cortical

density. However, the differences in the results between the two methods were in the main much smaller than the differences in the results between the two highly divergent study groups. Finally, in ProMo, bone scanning of the frailest patients was challenging, and consequently the amount of missing data was considerable.

6.5 Implications and future perspectives

This dissertation provides new, valuable, and detailed information on the adaptive pattern of aging bone to physical exercise and the longitudinal associations of physical function and exercise with bone aging and post-hip fracture bone deterioration. The unique focus on middle-aged and older athletes and older adults with hip fracture addressed the knowledge gap on the osteogenic potential of exercise in people at the opposite ends of the physical activity and bone health spectrums. By combining and contrasting the results obtained for the two divergent groups, the current research model expands our understanding on bone adaptation and maintenance during aging and provides new insight into the increasing problem of osteoporosis and fractures. The study revealed positive effects on mid-tibial cross-sectional geometry and strength after only 20 weeks' combined high-intensity strength and sprint training, and hence, challenges the idea that physical exercise is unlikely to enhance bone properties among older people who already have a strong bone structure. Moreover, regular intensive training maintained or even improved bone during aging, whereas home-based weight-bearing exercises, on the contrary, were unable to prevent post-hip fracture-related bone weakening. Overall, these findings suggest that with regular high-intensity loading, given the muscular capacity to effectively load bones, the adaptability of bone structure can be maintained with aging, and hence that it is possible to counteract the age-related loss in bone structure, density and strength. Preserving bone through physical exercise after a hip fracture, however, seems unlikely, at least if physical function and muscular capacity are low.

More research is needed to find out whether fragile bones, such as those in older adults with hip fracture, are able to adapt to increased physical loading, and what type of exercise would be safe, feasible and effective. Acknowledgement of the risk factors for accelerated post-fracture bone loss could assist in developing interventions and care to promote bone health and overall recovery. The intensive training programs of athletes cannot, as such, be recommended for ordinary aging people. However, masters athletes serve as good examples of the upper limits of physical performance and the adaptability of musculoskeletal health. Strength training and other high-intensity training have become increasingly popular among older people, and exercises targeted at improving muscle force generating capacity are highly recommended at all ages and at both ends of the physical activity and bone health spectrum. Maximizing muscle power is especially important in falls prevention, and hence in the

prevention of hip fractures. Further studies should investigate the effects of combined strength and impact training programs of longer duration on aging people in general and in those at increased risk for fracture. More research is also needed on the effects of combined training on age-related changes at the clinically important proximal femur site, also in female athletes and in sedentary aging people.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings of this study are:

1. A 20-week high-intensity strength and sprint training program had positive effects on mid-tibia structure and strength in middle-aged and older male sprint athletes. The effects were more pronounced in the most compliant athletes, suggesting that novel, intensive training, even of short duration, can strengthen aging bones, even in subjects with a long-term high-impact training background.

2. Maintenance of regular strength and sprint training over time was associated with maintained distal tibia trabecular density, bone mass and compressive strength, and with improved tibial mid-shaft structure and bone mass.

3. A yearlong home-based rehabilitation program aimed at mobility recovery was unable to prevent post-hip fractural bone deterioration in older men and women. Trabecular and cortical bone traits (structure, density and strength) continued to weaken in both legs but especially in the leg on the fractured side.

4. Lower physical function (as measured with SPPB and difficulty in walking outdoors) was predictive of greater decline in distal tibia bone density and strength in both legs. Lower lean bone mass was associated with greater decline in distal tibia density in both legs. At the mid-tibia site, a lower SPPB score and lower LBM were associated with greater decline in SSI on the fractured side only.

YHTEENVETO (SUMMARY IN FINNISH)

Vanhenevan luuston vasteet liikuntaharjoitteluun: ikääntyvät urheilijat ja lonkkamurtumapotilaat tutkimusmallina

Luuston lujuusominaisuudet heikkenevät ikäännyttäessä. Osa ikääntymiseen liittyvästä luuston heikkenemisestä selittyy todennäköisesti luustoa kuormittavan liikunnan vähenemisellä. Erityisen suurta luuston haurastuminen on lonkkamurtuman jälkeen, jolloin myös toimintakyky tyypillisesti alenee ja liikkuminen vähenee. Intensiivinen voima- ja tehoharjoittelu sekä kehon painoa kannatteleva, luuta iskutyyppisesti kuormittava liikunta ovat luuston kannalta tehokkaita liikuntamuotoja. Tällainen harjoittelu voi kuitenkin olla liian rajua harjoitteluun tottumattomille iäkkäille henkilöille, eikä ikääntyvän luun mukautumiskyvystä intensiiviseen liikuntaan ole tarpeeksi tietoa. Toistaiseksi ei myöskään tiedetä, voidaanko liikunnan avulla ylläpitää tai kehittää erityisen haurasluisten ja heikkokuntoisten iäkkäiden henkilöiden, kuten lonkkamurtumapotilaiden luuston ominaisuuksia. Tämän tutkimuksen tarkoituksena oli selvittää vanhenevan luuston mukautumiskykyä fyysiseen kuormitukseen toimintakyvyn ja luun terveyden eri ääripäissä. Tutkimuksessa selvitettiin maksimaalisen ja räjähtävän voima- ja iskutyyppisen harjoittelun vaikutusta pitkään harjoitelleiden, ikääntyvien pikajuoksijoiden luuston lujuusominaisuuksiin sekä sitä, voidaanko säännöllisellä, intensiivisellä harjoittelulla vastustaa luuston ikääntymismuutoksia. Lisäksi tutkittiin, voidaanko liikkumiskyvyn palautumiseen tähtäävällä kotikuntoutuksella estää tai hidastaa lonkkamurtuman jälkeistä luuston heikkenemistä sekä selvitettiin toimintakyvyn ja lihasten kunnon yhteyttä murtuman jälkeisiin luustomuutoksiin.

Tutkimus hyödynsi Jyväskylän yliopiston liikuntatieteellisen tiedekunnan ja Gerontologian tutkimuskeskuksen kahden tutkimusprojektin aineistoja. Athlete Aging Study (Athlas) sisälsi 20 viikon satunnaistetun, kontrolloidun kokeen (RCT, n=72) ja 10-vuotisseurannan (n=69). Athlas-tutkimukseen osallistui 40-85-vuotiaita pikajuoksijamiehiä, joilla oli pitkä harjoittelutausta. Promoting Mobility after Hip Fracture (ProMo) oli 12 kuukauden RCT, johon osallistui 81 lonkkamurtuman vuoksi äskettäin leikattua, yli 60-vuotiasta miestä ja naista. Lonkkamurtumapotilaiden kotikuntoutusohjelma sisälsi vastuskuminauhoin toteutettua voimaharjoittelua (3 krt/vk) sekä tasapainoharjoittelua ja toiminnallisia harjoitteita, kuten kävelyä ja portaiden nousua (2-3 krt/vk). Urheilijoiden harjoitteluohjelma puolestaan koostui pikajuoksun lajiharjoittelusta (2 krt/vk) sekä maksimaalisesta ja räjähtävästä voima- ja hyppelyharjoittelusta (2 krt/vk). Sääriluun poikkileikkausgeometriaa, tiheyttä ja laskennallista lujuutta selvitettiin molemmissa tutkimuksissa perifeerisellä tietokonetomografialla. Lonkkamurtumapotilaiden fyysistä toimintakykyä selvitettiin lyhyellä fyysisen suorituskyvyn testistöllä sekä koetuilla ulkona liikkumisen vaikeuksilla. Lihasmassan mittarina käytettiin bioimpendanssimenetelmällä mitattua rasvatonta kehonpainoa.

20 viikon intensiivinen voima- ja pikajuoksuharjoitteluohjelma paransi urheilijoiden sääriluun varren geometrisia ominaisuuksia ja taivutuslujuutta verrattuna kontrolliryhmään, joka jatkoi omaa pikajuoksupainotteista harjoitteluaan. 10-vuotisseurannassa havaittiin, että säännöllinen voima- ja pikajuoksuharjoittelu oli yhteydessä ylläpysyneeseen tai jopa parantuneeseen sääriluun varren poikkileikkausgeometriaan ja luumassaan, sekä ylläpysyneeseen sääriluun distaaliosan luumassaan, tiheyteen ja lujuuteen. Harjoittelun lopettaneiden/harjoittelua vähentäneiden ryhmässä luuston ominaisuudet sen sijaan heikkenivät seurannan aikana. Vuoden kestäneellä kotikuntoutuksella ei ollut vaikutusta lonkkamurtumapotilaiden sääriluun ominaisuuksiin. Sääriluun varren ja distaaliosan tiheys, lujuus ja geometriset ominaisuuden heikkenivät murtuman jälkeisen vuoden aikana sekä murtuneessa että terveessä jalassa. Heikompi toimintakyky ja alempi kehon rasvaton paino ennustivat luun distaaliosan ominaisuuksien suurempaa heikkenemistä molemmissa jaloissa.

Tutkimuksen tulokset viittaavat siihen, että intensiivinen harjoittelu ylläpitää terveen luuston mukautumiskykyä ja vastustaa ikääntymiseen liittyvää luuston heikkenemistä. Tehokkaalla ja luuta kohdennetusti kuormittavalla harjoitusärsykkeellä voidaan saada positiivisia vaikutuksia ikääntyvän luun geometrisiin ominaisuuksiin ja lujuuteen jo varsin lyhyessä ajassa. Kotikuntoutus ei sen sijaan kyennyt vastustamaan lonkkamurtuman jälkeistä luuston haurastumista. Hyvä fyysinen toimintakyky ja lihasten kunto näyttäisivät kuitenkin olevan avainasemassa luuston kunnon ylläpysymiselle myös haurasluisilla henkilöillä, kuten lonkkamurtumapotilailla. Lisää tutkimuksia tarvitaan selvittämään, voidaanko liikunnalla vaikuttaa haurasluisten, heikkokuntoisten iäkkäiden henkilöiden, kuten lonkkamurtumapotilaiden luuston ominaisuuksiin, ja minkälainen harjoittelu olisi sopivaa ja tehokasta. Vaikka urheilijoiden harjoittelu ei sellaisenaan sovellu kaikille ikääntyneille, urheilijat toimivat hyvinä esimerkkeinä tuki- ja liikuntaelimistön kunnon ylärajoista ja pitkäaikaisen harjoittelun yhteyksistä elimistön vanhenemiseen. Urheilijoiden harjoitteita voitaisiin soveltaa ikääntyvien liikuntaohjelmissa ennen toiminnanvajausten ilmenemistä ja siten edesauttaa tuki- ja liikuntaelimistön kunnon ylläpysymistä. Oikein toteutettu voima- ja tehoharjoittelu on suositeltavaa kaiken ikäisille.

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ORIGINAL PAPERS

I

EFFECTS OF A 20-WEEK HIGH-INTENSITY STRENGTH AND SPRINT TRAINING PROGRAM ON TIBIAL BONE STRUCTURE AND STRENGTH IN MIDDLE-AGED AND OLDER MALE SPRINT ATHLETES: A RANDOMIZED CONTROLLED TRIAL

by

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ORIGINAL ARTICLE

Effects of a 20-week high-intensity strength and sprint training program on tibial bone structure and strength in middle-aged and older male sprint athletes: a randomized controlled trial

T. H. Suominen[1] · M. T. Korhonen[1] · M. Alén[2] · A. Heinonen[3] · A. Mero[3] · T. Törmäkangas[1] · H. Suominen[3]

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Abstract
Summary This randomized, controlled, high-intensity strength and sprint training trial in middle-aged and older male sprint athletes showed significant improvements in mid-tibial structure and strength. The study reveals the adaptability of aging bone, suggesting that through a novel, intensive training stimulus it is possible to strengthen bones during aging.
Introduction High-load, high-speed and impact-type exercise may be an efficient way of improving bone strength even in old age. We evaluated the effects of combined strength and sprint training on indices of bone health in competitive masters athletes, who serve as a group of older people who are likely to be able to participate in vigorous exercise of this kind.
Methods Seventy-two men (age 40–85) were randomized into an experimental (EX, $n = 40$) and a control (CTRL, $n = 32$) group. EX participated in a 20-week program combining heavy and explosive strength exercises with sprint training. CTRL maintained their usual, run-based sprint training schedules. Bone structural, strength and densitometric parameters were assessed by peripheral QCT at the distal tibia and tibial midshaft.
Results The intervention had no effects on distal tibia bone traits. At the mid-tibia, the mean difference in the change in cortical thickness (Th_{CO}) in EX compared to CTRL was 2.0% ($p = 0.007$). The changes in structure and strength were more pronounced in the most compliant athletes (training adherence >75%). Compared to CTRL, total and cortical cross-sectional area, Th_{CO}, and the area and density-weighted moments of inertia for the direction of the smallest flexural rigidity (I_{minA}, I_{minD}) increased in EX by 1.6–3.2% ($p = 0.023$–0.006). Polar mass distribution analysis revealed increased BMC at the anteromedial site, whereas vBMD decreased ($p = 0.035$–0.043).
Conclusions Intensive strength and sprint training improves mid-tibia structure and strength in middle-aged and older male sprint athletes, suggesting that in the presence of high-intensity loading exercise, the adaptability of the bone structure is maintained during aging.

Keywords Aging · BMD · Bone pQCT · Exercise · High-impact training · Masters athlete · Strength training

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✉ T. H. Suominen
tuuli.suominen@jyu.fi

[1] Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

[2] Department of Medical Rehabilitation, Oulu University Hospital and Center for Life Course Health Research, University of Oulu, Oulu, Finland

[3] Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

Introduction

Exercise has shown good potential to strengthen bones by increasing bone mass, structure and strength at loaded sites across the age spectrum. Previous studies have indicated that the most osteogenic exercise includes high-magnitude loads that are unusual, dynamic, rapid, multidirectional and applied at intervals [1–5]. Older people with a low level of physical functioning and reduced bone and muscle strength may not, however, tolerate or be willing or able to participate in exercise at the intensity required to stimulate osteogenic adaptation. Consequently, the adaptability of aging bone to intensive exercise remains unclear.

Observational studies have shown that middle-aged and older masters athletes with a high-impact training background have greater bone strength than non-active counterparts [6, 7], or even a younger physically active reference group [8]. According to these studies, the adaptation of bone strength in adult bone shafts appears to be more evident in bone geometry than in volumetric bone mineral density (vBMD) [8, 9]. However, in distal parts of the bone, compressive strength is also related to higher trabecular vBMD [10]. Structural adaptation in strength and sprint trained athletes manifests as greater cortical area and thickness at the loaded sites [6, 8, 9, 11]. In addition, bone mass distribution analyses have revealed higher site-specific cortical bone mass at the tibial and femoral mid-shaft, which may contribute to higher direction-specific bending strength [8–10, 12].

The experimental evidence on the effects of exercise on bone structure and strength in older people is scarce and somewhat conflicting. A previous meta-analysis [13] found no significant exercise effects on bone strength, which may partly be explained by the short duration and inadequate power of the few published trials, along with the use of non-athletic study populations and less intensive training programs. Since then, studies on middle-aged and older people have found positive, site-specific effects on proximal femoral bone mass after impact training [14] but no effects on mid-femoral or mid-tibial structure and strength after strength training or combined strength and impact training [15, 16]. To date, no attempts have been made to investigate the effects of intensive strength, sprint and plyometric training on bone in older athletes. Using an experimental design with masters athletes who are likely to be able to participate in vigorous exercise of this kind, our study can provide valuable insight into the osteogenic potential of specific types of training among older people. We hypothesized that a 20-week training program combining heavy and explosive strength exercises with sprint training would increase bone strength in middle-aged and older masters athletes by improving the geometrical properties of the tibial shaft and by adding density in the distal tibia. In light of the evidence from cross-sectional athlete studies, the main focus was on the structural adaptation of bone.

Methods

Subjects and study design

This study was a 20-week randomized controlled trial (ISRCTN17271498; Fig. 1). The study was part of a larger research program on the effects of age and long-term sprint training on musculoskeletal characteristics and neuromuscular function among male masters athletes [8, 17]. Athletes with a long-term training background and success in international or national masters sprint events (n = 111) were contacted by a personal letter. A detailed questionnaire on current and former training, competition performance, and injuries or diseases hindering physical training was mailed along with the recruitment letter. After assessment of eligibility, based on the questionnaire responses, a total of 83 voluntary athletes were invited to participate in the baseline measurements. The inclusion criteria were age ≥40, and ongoing systematic training and competing. Exclusion criteria included uncontrolled medical conditions or musculoskeletal disorders contraindicating exercise, medical conditions which would limit training program participation, and medications affecting bone metabolism. The health history and current health of those invited to the baseline measurements was assessed in more detail by means of a mailed questionnaire and, along with training status, confirmed in a short interview and clinical examination including resting electrocardiogram (ECG, athletes aged ≥55) and blood pressure measurements. For those under age 55, resting ECG was obtained at the athlete's own request or based on a physician's assessment (n = 9).

Eleven athletes were excluded for medical reasons contraindicating intensive training (cardiovascular disease, hip osteoarthritis, rheumatoid arthritis of the spine, Parkinson's disease, prostate cancer; n = 10) or unwillingness to participate (n = 1). Among the participants accepted for the trial, 14 presented with chronic conditions (asthma, n = 3; celiac disease, n = 1; type 1 diabetes, n = 1; hypertension, n = 7; hypothyroidism, n = 2); however, all conditions had been adequately diagnosed by their own physician and thereafter treated with good response.

After the baseline measurements, the athletes were randomized into an experimental (EX, n = 40) and a control (CTRL, n = 32) group. First, a list of participants (sampling frame) was constructed, with subjects stratified by age. Next, lots were drawn manually, separately for each 10-year age group. Numbered and folded pieces of paper were well-shaken and blindly drawn one by one from a box for each subject in the sampling frame. To compensate for the possibility of a higher drop-out rate and larger variance in the results, in each age group a higher number of subjects was assigned to EX than to CTRL. Three subjects entered the trial after the initial randomization had been performed and thus were separately randomized by simple randomization. The randomization was performed by HS and MK. All the bone outcome assessors were blinded to the treatment-group assignment.

The experimental group participated in a 20-week program combining heavy and explosive strength exercises with sprint training. Controls were asked to maintain their usual, mostly run-based, sprint training schedules. Follow-up measurements were completed immediately after the training period. Written informed consent was obtained from all subjects prior to participation in the study. The study was approved by the University of Jyväskylä Ethical Committee and conformed with the principles of the Declaration of Helsinki.

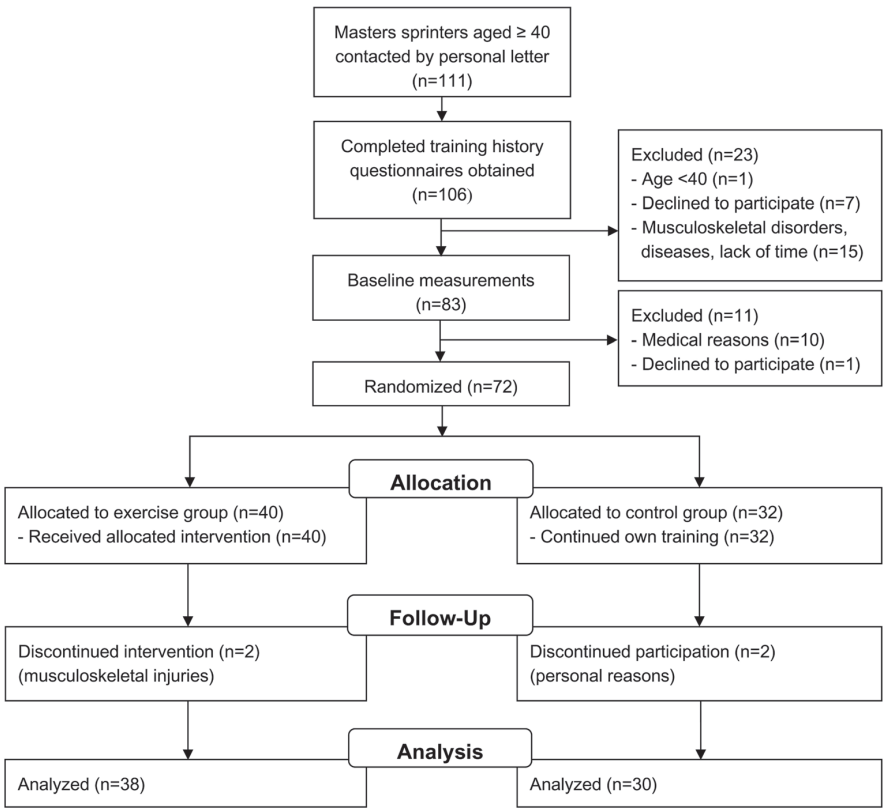

Fig. 1 Flowchart of the study

Periodized training program

The combined strength and sprint training program, which has been described in detail in our previous article [18], was collaboratively designed by researchers and coaches, and utilized knowledge obtained from earlier studies in young adult athletes [19–21]. Although the main initial focus of the training program was to improve sprint performance and muscle strength, the osteogenic effect was also considered. The 20-week program was designed to fit into the training and competitive seasons of the athletes, and aimed at maximizing their performance at major championships. To reduce the potential for overtraining and to optimize adaptation to training, attention was paid to the proper periodization of training (Supplementary Fig. 1). The program consisted of two 11- and 9-week periods that were further divided into three phases of 3–4 weeks with a different intensity, volume and type of training. The first 4 weeks of strength training consisted of strength endurance and hypertrophy exercises. In the second and third phases, maximal strength and explosive strength exercises (weightlifting and plyometrics) alternated. During the latter half of the training program, the three-phase protocol was repeated with a progressive increase in training intensity. The strength training sessions focused on the leg extensor and hamstring muscle groups, with a limited number of exercises for the upper body and trunk. Plyometric exercises progressed from lower-intensity vertical jumps to higher-intensity horizontal bounding exercises. The sprint training program was similar during both training periods, progressing from speed-endurance to maximum speed exercises. Both the strength and sprint training were performed twice weekly on non-consecutive days. This was expected to provide adequate overload without overtraining or injuries, as well as to provide a sufficient quantity of strength training, which was a novel training stimulus for these athletes. The plyometric exercises were performed at the beginning of the speed training session, 1–2 times per week.

Because of the wide age range of the subjects, and the fact that most of them were not accustomed to heavy strength training, the subjects were divided into two age groups (40–64 and 65–85 years) receiving slightly different strength training programs. The intensity of the strength training was, in part, slightly lower in the older age group (more repetitions, lower resistance).

Training programs, along with written, pictorial and videotaped instructions for the different exercises, were mailed to EX. Both EX and CTRL filled out detailed training logs (describing sets, repetitions, loads, distances and times) to

monitor progress and to enhance motivation for maximal effort. Based on the logs (collected every 5th week), total and weekly numbers of training sessions in the different training modes were calculated for each participant. The training adherence rate of the EX group members was calculated as the percentage of the training session successfully completed. Field tests for running performance and muscle power (data not shown) were organized in weeks 5, 10 and 15 to obtain feedback on the athlete's training status and degree of progress.

Peripheral quantitative computed tomography (pQCT)

Properties of the distal tibia and tibial shaft of the dominant leg (the leg used for take-off in a one-footed jump) were determined by pQCT (XCT-2000, Stratec Medizintechnik, Pforzheim, Germany) according to the methods described earlier [8, 10]. The distal tibia was defined as 5% and tibial shaft as 50% of the measured tibial length proximal to the distal end plate. Tibial length was defined as the distance between the lateral malleolus and the condyle of tibia. Cross-sectional pQCT images included a single (2-mm) axial slice with pixel size of 0.8 × 0.8 mm. The images were analyzed with software designed for analyzing cross-sectional CT images (Geanie 2.1; Commit Ltd., Espoo, Finland). A threshold of 169 mg/cm^3 for the distal tibia and 280 mg/cm^3 for the midshaft site was used to determine the outer bone border. Separation of trabecular and cortical bone was performed using an automatic contour detection algorithm (K-mode). At the distal site, bone marrow was included in the analyses, whereas at the midshaft site bone marrow was excluded by applying a threshold of 100 mg/cm^3.

The main parameters for the midshaft site were total cross-sectional area (CSA_{TOT}, mm^2), cortical CSA (CSA_{CO}, mm^2), mean cortical wall thickness (Th_{CO}, mm) and area moments of inertia (I_{minA}, I_{maxA} and I_{polarA}, mm^4). I_{minA} and I_{maxA} reflect the bone's resistance to bending in the direction of the smallest and greatest flexural rigidity, while I_{polarA} refers to bending and torsional rigidity around the neutral axis of the bone. Secondary parameters for the midshaft site were total bone mineral content (BMC_{TOT}, mg/mm), total volumetric bone mineral density ($vBMD_{TOT}$, mg/cm^3), cortical vBMD ($vBMD_{CO}$) and density-weighted moments of inertia (I_{minD}, I_{maxD} and I_{polarD}, mg*cm). In addition, BMC was further analyzed as the polar distribution of bone mineral mass around its center, using 5° steps that were subsequently averaged into eight 45° sectors: anterior (A), anteromedial (A-M), medial (M), posteromedial (P-M), posterior (P), posterolateral (P-L), lateral (L) and anterolateral (A-L) (Supplementary Fig. 2). For the distal tibia, BMC_{TOT}, $vBMD_{TOT}$, trabecular vBMD ($vBMD_{TRAB}$), CSA_{TOT}, trabecular CSA (CSA_{TRAB}) and a compressive bone strength index (BSI, g^2/cm^4 = $vBMD_{TOT}^2 \times CSA_{TOT}$) [22, 23] were determined. The root mean square coefficient of variation (CV_{RMS}) for the BMD, structure and strength index measurements in our laboratory ranges from 0.4 to 1.6% [24]. In terms of least significant change (LSC = 2.77 × CV_{RMS}) [25], which refers to a change greater than the precision error for a single individual, this corresponds to a range of 1.2–4.4%.

Anthropometry, calcium and vitamin D intake, hormone measurements and physical performance

Body height and weight were measured using standard procedures. Lean body mass (LBM, kg) was assessed with a bioimpedance device using the manufacturer's equations (Spectrum II, RJL Systems, Detroit, MI, USA). Before the measurements, the subjects had fasted for at least 3 h. Calcium and vitamin D intakes were obtained from 5-day food diaries kept in week 15. The diaries were analyzed by Micro Nutrica 3.0 software (Social Insurance Institution of Finland). Blood samples were drawn from the antecubital vein after an overnight fast. Specimens were centrifuged (3500 rpm, 4 °C for 10 min) and frozen at −75 °C until assayed. Serum concentration of total testosterone (total T, nmol/L) was analyzed by applying the Immulite chemiluminescent method (Diagnostic Products Corporation, Los Angeles, CA). The intra-assay CV for total T was 5.5%. Maximal 60-m running times on an indoor synthetic track with spiked shoes were obtained using double-beam photocell gates (starting line 0.7 m behind the first photocell gates). Own standing start without commands was used.

Statistical analysis

Mean values and standard deviations (SD) were calculated using standard procedures. The main outcome variables were analyzed according to the intention-to-treat principle. Baseline characteristics and training characteristics of the EX and CTRL groups during the experimental period were compared by independent samples t test. For variables that were not normally distributed, the Mann-Whitney U test was applied instead of the t test. The effect of the intervention was examined by means of repeated measures ANOVA. If the significance of the interaction of the effects of group and time was $p < 0.1$, an independent samples t test was used to test the differences in percentage changes between EX and CTRL, and separately in the two age groups [40–64 (EX, $n = 21$; CTRL, $n = 14$) and 65–85 ($n = 17$ and 16, respectively) years]. The effect of the intervention was also examined by per protocol analysis, in which case only subjects who had completed over 75% of the assigned 75 strength and speed exercises were chosen from the experimental group. Data were analyzed using SPSS 22.0 software (IBM, NY, USA) with the significance level set at $p < 0.05$.

Power analysis was conducted by setting the significance level at 0.05 and power at 80%. We used a sequential method of sample size calculation that permits having more than one primary outcome [26, 27]. The six primary outcomes were expected to be highly dependent and hence, based on the assumed effectiveness of the intervention on the variables, the dependency measure was set to range between 0.90 and 0.95. The follow-up correlations were likely to be high and we set these to be approximately within the range 0.975–0.977. Sample size was then calculated by allocating the significance level sequentially for the outcome variables, starting from the outcome likely to require the largest sample size (CSA_{TOT}, 2% difference, pilot data standard deviation: 56) and proceeding to CSA_{CO} (difference: 2%, pilot data SD: 50), Th_{CO} (difference: 2.5%, pilot data SD 0.69), I_{polarA} (difference: 3.5%, pilot data SD: 14,652), I_{minA} (difference: 3.5%, pilot data SD: 4053) and, finally, I_{maxA} (difference: 3.7, pilot data SD: 11,636). These settings, with the allocated significance level of 0.03 for each outcome variable, led to sample sizes varying between 25 and 38 for the intervention and control groups.

Results

No differences were observed at baseline between EX and CTRL in physical characteristics or training background (Table 1). Training programs during the year preceding the intervention mainly consisted of sprint training, speed-endurance training and plyometric exercises. Strength training was performed by 80% of the athletes. No age-group differences were observed in the training programs of the preceding year, except in the amount of strength training, which was significantly higher in the group aged 40–64 than in the group aged 65–85 [1.6 (1.5) vs. 0.8 (0.9) h/week, $p = 0.018$]. The 5-day food-intake diaries collected during the experimental period showed no differences between EX and CTRL in calcium or vitamin D intake. In the per protocol analysis, no between-group differences were observed in baseline characteristics. The intervention had no effect on body weight, LBM or total T. The 60-m trial times of the EX ($n = 30$) group improved from 8.54 (0.76) to 8.50 (0.91) s, whereas in CTRL ($n = 29$) the corresponding times were 8.40 (0.61) and 8.50 (0.61) s (group × time interaction $p = 0.025$).

The intervention did not cause major injuries or health problems. Minor musculoskeletal discomfort (transient muscle strains and joint sprains) were reported in both the EX ($n = 16$) and CTRL ($n = 9$) groups during testing, training and competitions. Two EX participants withdrew from the study due to persistent musculoskeletal disorder (knee pain, ankle pain due to pre-existing injury; unrelated to the exercise intervention). Two controls dropped out for personal reasons.

Table 1 Baseline physical and training characteristics, and calcium and vitamin D intake

	Experimental group ($n = 40$)	Control group ($n = 32$)
Age (years)	60.2 (11.8)	61.8 (12.1)
Height (cm)	175.4 (6.0)	173.1 (6.9)
Weight (kg)	73.2 (7.5)	73.8 (9.0)
Lean body mass (kg)	63.3 (5.6)	62.7 (7.8)
Total testosterone (nmol/L)	16.6 (4.5)[b]	16.7 (6.3)[c]
Training background (years)	34.5 (16.0)[d]	30.3 (16.5)[c]
Training (sessions/week)	4.3 (1.3)	4.2 (1.4)
Training (h/week)	6.5 (2.9)	6.8 (3.7)
Strength training (h/week)	1.2 (1.2)	1.3 (1.5)
Sprint training and plyometrics (h/week)	3.2 (2.3)	3.1 (2.3)
Calcium intake (mg/day)[a]	1378 (433)[e]	1248 (460)[f]
Vitamin D intake (μg/day)[a]	7.6 (4.9)[e]	9.8 (7.3)[f]

Values are means (SD).

[a] Obtained from the 5-day food diaries kept during week 15

[b] $n = 39$

[c] $n = 31$

[d] $n = 36$

[e] $n = 30$

[f] $n = 24$

Training adherence

In EX, the overall training adherence rate was 68 (26) % [51 (20) strength and speed training sessions completed out of the 75 prescribed, $n = 37$]. For strength training, it was 64 (30) % [23 (11) sessions], for sprint training 69 (30) % [27 (12) sessions] and for the plyometric exercises 52 (32) % [17 (10) sessions]. The CTRL group maintained their own habitual training programs, which included 46 (18) strength and speed training sessions [19 (10) strength training sessions, 30 (14) sprint training sessions and 11 (12) plyometric exercise sessions, $n = 29$]. The strength training of the controls consisted mainly of strength endurance and hypertrophy exercises.

The number of active training weeks varied across the EX and CTRL groups [17 (4.6) and 18 (2.8), respectively]. During the active weeks, the EX participants reported a significantly higher average number of strength [1.3 (0.5) vs. 1.0 (0.5), $p = 0.034$] and plyometric training sessions [0.9 (0.5) vs. 0.6 (0.6), $p = 0.035$] than controls.

Bone traits

At baseline, no differences were found in bone traits between EX and CTRL, except in $vBMD_{TOT}$ and $vBMD_{CO}$ of the tibial midshaft, which were 2–3% higher in EX ($p = 0.002$ and 0.001, respectively). The intervention had no effect on distal tibia bone traits (Supplementary Table 1). The effect of the

training on the tibial midshaft is shown in Table 2, Supplementary Table 2 and in Fig. 2. The average difference in change in Th_{CO} in EX compared to CTRL was 2.0% (p = 0.007) across the whole EX group and 2.8% (p = 0.008) in the group aged 65–85 (EX, n = 17; CTRL, n = 16). The corresponding differences in I_{minA} were 1.9% (p = 0.034) across the whole EX group and 2.8% (p = 0.031) in the group aged 40–64 (n = 21 and 14, respectively).

Per protocol analysis

As in intention-to-treat analysis, no changes were detected in the distal tibia bone traits. The effect of the training on the tibial midshaft bone traits is shown in Tables 3 and 4 and in Fig. 2. In the EX compared to CTRL group, CSA_{TOT} increased by 1.6% (p = 0.013), CSA_{CO} by 1.8% (p = 0.007), and Th_{CO} by 2.6% (p = 0.012). In the area and density-weighted moments of inertia, the increase in favor of EX was 3.2% for I_{minA} (p = 0.006), 1.8% for I_{minD} (p = 0.023), and 2.0% for I_{polarA} (p = 0.035). In the EX compared to CTRL group, BMC_{TOT} increased by 0.7% (p = 0.017), whereas the changes in density favored CTRL ($vBMD_{TOT}$ 0.9%, p = 0.035 and $vBMD_{CO}$ 0.8%, p = 0.043). The polar mass distribution analysis revealed a significant group × time interaction at the A-M site. In EX compared to CTRL, $BMC_{A\text{-}M}$ increased by 2.2% (p = 0.051).

Discussion

As hypothesized, this 20-week randomized, controlled, high-intensity strength and sprint training trial in middle-aged and older male sprint athletes showed significant, albeit modest changes in tibial midshaft structure and strength. The changes were more pronounced in the most compliant athletes, which indicates that novel, intensive training, even of short duration, can strengthen aging bones, even in subjects with a long-term high-impact training background. The intervention had no effect on distal tibia bone traits.

Table 2 Effects of strength and sprint training on tibial mid-shaft bone traits. Intention-to-treat analysis

	Experimental group (n = 38)		Control group (n = 30)		ANOVA (p)		
	Baseline	6 months	Baseline	6 months	Group	Time	Group × time
CSA_{TOT} (mm^2)	514 (57)	517 (56)	521 (55)	521 (56)	0.666	0.336	0.158
CSA_{CO} (mm^2)	416 (48)	418 (47)	414 (52)	413 (54)	0.794	0.496	0.071
Th_{CO} (mm)	5.35 (0.64)	5.39 (0.63)	5.27 (0.74)	5.20 (0.75)	0.434	0.495	0.008
I_{maxA} (mm^4)	47,320 (11,300)	47,590 (11,050)	48,220 (12,030)	48,350 (12,240)	0.771	0.255	0.675
I_{minA} (mm^4)	17,520 (4137)	17,800 (4210)	18,550 (3774)	18,530 (3894)	0.371	0.074	0.041
I_{polarA} (mm^4)	64,840 (14,370)	65,390 (14,160)	66,770 (15,040)	66,880 (15,410)	0.635	0.143	0.314
BMC_{TOT} (mg/mm)	511 (59)	513 (58)	504 (62)	505 (62)	0.605	0.038	0.211
$vBMD_{TOT}$ (mg/cm^3)	995 (38)	994 (38)	967 (46)	969 (44)	0.009	0.850	0.223
$vBMD_{CO}$ (mg/cm^3)	1103 (20)	1102 (19)	1085 (26)	1088 (22)	0.003	0.664	0.137
I_{maxD} (mg*cm)	4959 (1210)	4980 (1176)	4967 (1280)	4989 (1291)	0.977	0.064	0.947
I_{minD} (mg*cm)	1792 (425)	1813 (426)	1858 (385)	1862 (392)	0.566	0.018	0.105
I_{polarD} (mg*cm)	6752 (1521)	6793 (1486)	6825 (1592)	6851 (1609)	0.862	0.027	0.609

Values are means (SD). The displayed p value denotes the main and interaction effects

CSA_{TOT} total cross-sectional area, CSA_{CO} cortical CSA, Th_{CO} cortical thickness, I_{maxA}, I_{minA}, I_{polarA} maximal, minimal and polar area moments of inertia, BMC_{TOT} total BMC, $vBMD_{TOT}$ total volumetric BMD, $vBMD_{CO}$ cortical vBMD, I_{maxD}, I_{minD}, I_{polarD} density-weighted maximal, minimal and polar moments of inertia

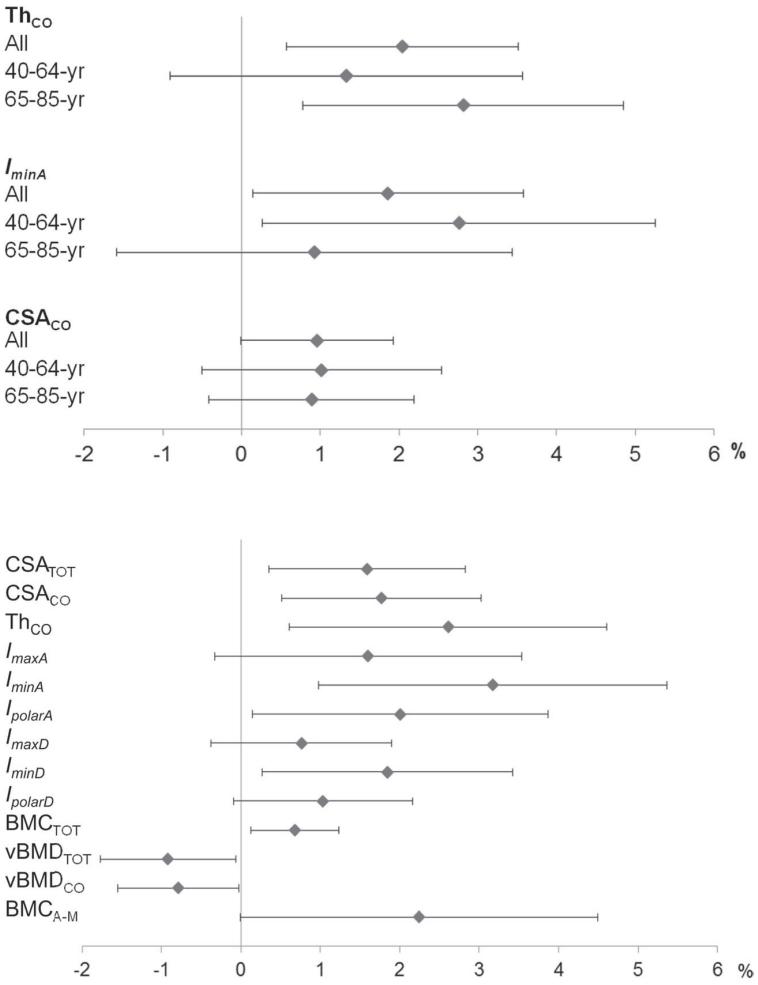

Fig. 2 The differences in changes in tibial midshaft bone traits after 20 weeks' high-intensity strength and sprint training. EX vs. CTRL (mean, 95% confidence interval). Intention-to-treat (*upper panel*) and per protocol analysis (*lower panel*)

The adaptation in this exercise training program, as in some previous studies [28–30], occurred in bone structure and, theoretically, in bending strength without increases in BMD. The greatest structural changes were observed in the cortical thickness of the tibial shaft, which accords with findings from previous observational athlete and twin studies [6–8, 10]. Th_{CO} increased slightly in the EX group, while in the CTRL group Th_{CO} decreased, which indicates that the training maintained rather than improved Th_{CO}. In addition, there was a tendency towards increased total and cortical CSA in the EX group; in the per protocol analysis, the increase was significant in both parameters.

Parallel results have also been observed in some intervention studies on premenopausal [31] and postmenopausal [28, 32, 33] women after 6 to 12 months' strength and/or impact training. Interventions targeting bone structure among older people are, however, scarce and comparison of the results is challenging due to variation in study populations, training programs, intervention duration and the bone sites measured. Ashe et al. [15] found no effect on mid-tibia vBMD, structure or strength in pretrained, postmenopausal women after resistance training for 1 year. Similarly, in the study by Kukuljan et al. [16] 18 months' combined high-intensity strength training and weight-bearing impact exercises had no effect on mid-femur or mid-tibia vBMD, structure or strength in 50- to 79-year-old men, despite an increase in femoral neck aBMD. In the present study, we detected changes in bone in subjects with prior exposure to vigorous exercise. In previous studies, conducted mainly on average older populations, the intensity of the strength and/or impact training might have been too low or the training might not have been progressive or specific for bone adaptation. The exercises performed in this study were characterized by high magnitude and/or a high strain rate, both of which are determinants of bone adaptation [5, 34]. The initial muscle structural and functional characteristics of the athletes were already clearly above average, and were further improved by the training program [18], probably reaching a level high enough to trigger adaptive response in bone.

Table 3 Effects of strength and sprint training on tibial mid-shaft bone traits. Per protocol analysis

	Experimental group (n = 16)		Control group (n = 30)		ANOVA (p)		
	Baseline	6 months	Baseline	6 months	Group	Time	Group × time
CSA_{TOT} (mm^2)	502 (60)	509 (60)	521 (55)	521 (56)	0.387	0.037	0.016
CSA_{CO} (mm^2)	408 (57)	413 (54)	414 (52)	413 (54)	0.851	0.070	0.008
Th_{CO} (mm)	5.31 (0.61)	5.39 (0.63)	5.27 (0.74)	5.20 (0.75)	0.609	0.909	0.010
I_{maxA} (mm^4)	46,533 (14,728)	48,840 (14,600)	48,220 (12,030)	48,350 (12,240)	0.731	0.060	0.181
I_{minA} (mm^4)	16,719 (4188)	17,178 (4137)	18,550 (3774))	18,530 (3894)	0.198	0.021	0.012
I_{polarA} (mm^4)	63,253 (17,878)	64,424 (17,552)	66,770 (15,040)	66,880 (15,410)	0.552	0.031	0.069
BMC_{TOT} (mg/mm)	504 (69)	508 (68)	504 (62)	505 (62)	0.947	0.003	0.020
$vBMD_{TOT}$ (mg/cm^3)	1002 (35)	995 (34)	967 (46)	969 (44)	0.019	0.243	0.030
$vBMD_{CO}$ (mg/cm^3)	1109 (20)	1103 (17)	1085) (26	1088 (22)	0.006	0.481	0.039
I_{maxD} (mg*cm)	4913 (1619)	4957 (1569)	4967 (1280)	4989 (1291)	0.921	0.016	0.405
I_{minD} (mg*cm)	1725 (442)	1757 (435)	1858 (385)	1862 (392)	0.348	0.008	0.038
I_{polarD} (mg*cm)	6638 (1961)	6714 (1905)	6825 (1592)	6851 (1609)	0.762	0.006	0.164

Values are means (SD). The displayed p value denotes the main and interaction effects

CSA_{TOT} total cross-sectional area, CSA_{CO} cortical CSA, Th_{CO} cortical thickness, I_{maxA}, I_{minA}, I_{polarA} maximal, minimal and polar area moments of inertia, BMC_{TOT} total BMC, $vBMD_{TOT}$ total volumetric BMD, $vBMD_{CO}$ cortical vBMD, I_{maxD}, I_{minD}, I_{polarD} density-weighted maximal, minimal and polar moments of inertia

The increased cortical thickness and cortical CSA observed in the present study was located by mass distribution analysis. According to the per protocol analysis, the increase in bone mass occurred in the A-M region. Cheng et al. [1] found that 12 months' hormone replacement therapy (HRT) and HRT combined with high-impact training mostly increased proximal tibia BMC in the A-P direction, resulting in increased bending resistance at the maximum axis (I_{max}). Similarly, in previous observational studies comparing athletes and reference subjects [8, 9], active and inactive monozygotic and dizygotic twins [10] or the jump and lead leg of jumping athletes [35], bone mass was greater in the A-P direction, as indicated by higher I_{max}. In the present study, adaptation in that direction might have already reached its maximum owing to the long-term training history of the athletes, as the intervention-related increase in bending resistance was observed largely at the minimum axis (I_{minA}).

The increase in the moments of inertia (I_{minA}, I_{minD} and I_{polarA}) was more pronounced in the per protocol analysis. It appears that the increase in bone strength did not occur unambiguously in the direction of the greatest or the smallest flexural rigidity, but in the A-P direction between the maximal and minimal moments (Supplementary Fig. 2), where, according to the bone mass distribution analyses, bone mass also increased. The increase in the moments of inertia suggests that the geometrical changes that occurred improved bending strength without accompanying improvements in BMD. Because, in the per protocol analysis, BMD decreased, the increase in BMC likely occurred due to the increase in bone area. These observations may indicate corticalization of the subcortical trabecular bone, which shows as thickened cortical bone without significant external expansion (p = 0.135, data not shown), that is, increased bone mass in an enlarged area (cortical wall thickness and cortical area), resulting in lower bone density. This result is in line with our earlier findings in premenopausal women [36].

As in some previous studies [15, 37–40] the lack of training-induced improvements in BMD could be attributable

Table 4 Effects of strength and sprint training on polar mass distribution of the tibial shaft. Per protocol analysis

	Experimental group (n = 16)		Control group (n = 30)		ANOVA (p)		
BMC	Baseline	6 months	Baseline	6 months	Group	Time	Group × time
A	890 (124)	908 (141)	881 (157)	879 (153)	0.683	0.319	0.247
A-M	329 (64)	336 (65)	342 (63)	341 (63)	0.647	0.085	0.046
M	469 (106)	471 (103)	514 (99)	512 (99)	0.169	0.960	0.523
P-M	852 (133)	851 (123)	816 (161)	822 (159)	0.481	0.540	0.317
P	736 (187)	747 (192)	732 (148)	729 (145)	0.830	0.399	0.121
P-L	531 (77)	537 (80)	547 (86)	547 (88)	0.619	0.478	0.479
L	320 (46)	324 (47)	325 (68)	327 (70)	0.850	0.294	0.689
A-L	913 (208)	905 (191)	888 (133)	891 (144)	0.694	0.759	0.470

Values are means (SD). The displayed p value denotes the main and interaction effects. BMC – values (mg/cm) are sum values of nine 5° sectors. (*A* anterior, *A-M* anteromedial, *M* medial, *P-M* posteromedial, *P* posterior, *P-L* posterolateral, *L* lateral, *A-L* anterolateral)

to normal or high pretraining BMD values. Another possible reason for the unchanged BMD in this study is the short duration of the intervention (20 weeks). Changes in bone geometry occur faster than changes in BMD. The bone mineralization cycle takes 3–4 months to complete, and therefore at least 6–8 months is needed to observe a new, measurable balance in BMD [41]. In the present study, bone mineralization might have occurred later, and hence, theoretically, the reason for our results could be earlier growth in bone size than in bone density, a phenomenon observed during adolescence [42]. As a result of this process, bone density decreases momentarily, as was also observed in the efficacy analysis of the present study. The decrease in cortical vBMD could also be related to exercise-induced microdamage that leads to targeted remodeling and thus increased intracortical porosity, as suggested by previous observational studies [6, 43].

In a study conducted on sedentary older people [32], impact-loading increased bone mass and estimated strength of the distal tibia. In the present study, adaptation occurred in the cross-sectional geometry of the tibial shaft without changes in the distal tibia or mid-tibia vBMD. This indicates that the adaptation occurred in response to bending strain derived from the increased and intensified strength and plyometric training rather than vertical compression from impact-loading, a phenomenon to which the athletes' bones might already have adapted. Most of the athletes were not accustomed to heavy strength exercises in their normal training routines. Previous strength training, especially among the older age group, might have focused more on light-resistance and high-repetition strength endurance exercises.

The amount of previous strength training was significantly lower in the older age group. Therefore, the overall intervention-induced increase in the amount and quality of the training might have been greater in the older age group than in the younger group. The latter group, in turn, was probably able to train harder than the older group, and the intensity of their intervention-related strength training, in particular, was higher. This could be related to their higher muscular capacity to produce bending strains. These possible differences in our athletes' previous training and the intervention-related training might account for the differences observed in the training response between the age groups. Compared to the CTRL group, Th_{CO} increased in the 65- to 85-year-olds but not in the 40- to 64-year-olds, whereas I_{minA} tended to increase in the younger but not in the older age group. Older age did not prevent adaptation, as changes were observed in both age groups. The testosterone values of our athletes were normal. No differences in total T values (baseline or follow-up) were observed between the age groups and the changes in bone variables were not related to the changes in total T levels (data not shown).

The strengths of this study include a randomized controlled trial design and the use of pQCT, which enables detection of changes in bone cross-sectional geometry and different bone tissue types. PQCT is precise and reproducible, and it can detect even the smallest changes in bone properties. Further strengths of our study include the unique focus on middle-aged and older male athletes as well as the examination of a novel training program combining high-intensity strength and sprint training with plyometric exercises. This study addresses

a knowledge gap in the research regarding bone-targeted exercise interventions for middle-aged and older men, and yields wholly novel information, as no corresponding studies conducted with a similar group have thus far been reported. Only few studies have demonstrated structural adaptation of the older skeleton. Most of the previous studies have utilized older populations with a low level of physical activity and reduced BMD. The competitive masters athletes studied here were both able and highly motivated to participate in vigorous training of a kind which could affect their bones, and the target intensities were likely to be achieved. Despite the minor musculoskeletal discomforts typical in competitive older athletes, all subjects were able to continue their training after a few days or weeks of modified or discontinued training. The intervention adherence was relatively high given the highly intensive, independently performed training program, and dropouts were few. The detailed bone mass distribution analyses can also be considered a strength, as only relatively few of these have been performed earlier.

The adaptations observed in this study were modest, which may have been attributable to the relatively short intervention period (may not have seen full mineralization in 20 weeks). In addition, the subjects had long-term training backgrounds and bones that were already strong, and thus major changes in bone properties during the relatively short study period were not expected. The study had multiple endpoints, which again means that the results have to be viewed with caution. The potential partial volume effect must also be considered, especially in relation to the area of trabecular bone. At the mid-shaft site, however, where the cortices are thick, this should not be an issue. The pQCT-related beam hardening may also have had some impact on our results, but probably not on the effect of the intervention. More detailed BMD analyses would have required a higher imaging resolution. We chose to use highly selected subjects and an active control group, who may have increased or intensified their training. The training practices of the intervention and control groups were rather similar, which may also have accounted for the modest adaptations observed. However, because an intervention-induced training effect was observed, it is likely that the quality and the intensity of the training of the intervention group changed more than that of the control group.

Our 20-week intervention challenges the idea that physical exercise is unlikely to enhance bone properties among older people who already have a strong bone structure. On the contrary, this study suggests that through physically active lifestyle the adaptability of the bone structure is maintained during aging. More research is needed on the effects of similar training programs of longer duration on aging people in general. Longer interventions would enable the examination of the maximal adaptive capacity of aging bone. Longer follow-ups would also allow examination of the possible interactions of strength and sprint training with the susceptibility to fractures. Although the intensive training program of athletes cannot, as such, be recommended for ordinary aging people, masters athletes serve as good examples of the upper limits of physical performance and the adaptability of musculoskeletal health.

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Compliance with ethical standards Written informed consent was obtained from all subjects prior to participation in the study. The study was approved by the University of Jyväskylä Ethical Committee and conformed with the principles of the Declaration of Helsinki.

Conflicts of interest None.

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SUPPLEMENTARY MATERIAL

These appendices have been provided by the authors to give readers additional supporting information about their work.

Supplement to: T. H. Suominen, M. T. Korhonen, M. Alén, A. Heinonen, A. Mero, T. Törmäkangas, H. Suominen. Effects of a 20-week high-intensity strength and sprint training program on tibial bone structure and strength in middle-aged and older male sprint athletes: a randomized controlled trial. Osteoporosis International

Corresponding author:
Tuuli Suominen
Gerontology Research Center, University of Jyväskylä, Jyväskylä, FINLAND,
Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, FINLAND
E-mail: tuuli.suominen@jyu.fi

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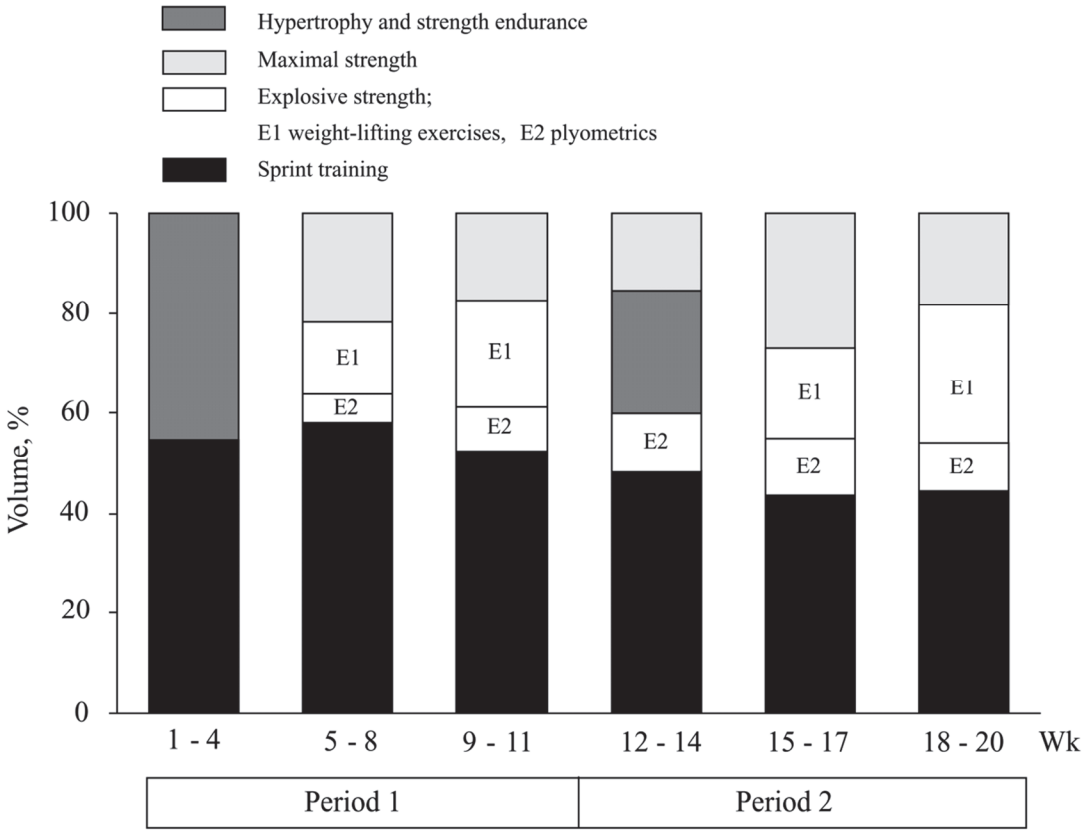
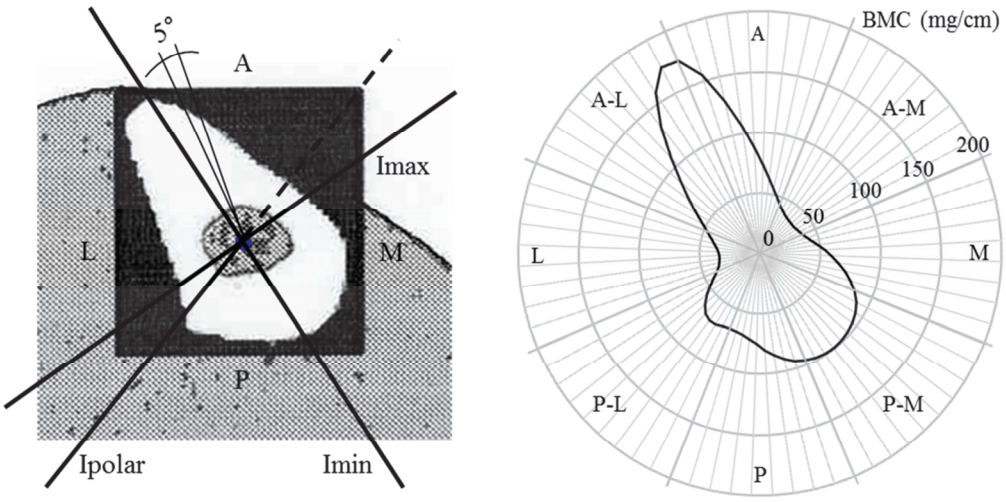
Appendix A



Supplementary Figure 1. Periodized training program and relative volumes of the different training modes. Adapted from Cristea et al.[15]

Appendix B



Supplementary Figure 2. Cross-sectional images of tibial shaft showing the directions of the axes of the I_{max}, I_{min} and I_{polar} moments, and the mean polar mass distribution curve of the athletes at baseline indicating angular distribution of bone mineral mass around the center of mass in 5° steps that were subsequently averaged into eight 45° sectors. (A = anterior, A-M = anteromedial, M = medial, P-M = posteromedial, P = posterior, P-L = posterolateral, L = lateral, A-L = anterolateral).

Appendix C

Supplementary Table 1. Effects of strength and sprint training on distal tibia bone traits. Intention-to-treat analysis.

	Experimental group (n = 38)		Control group (n = 30)		ANOVA (p)		
	Baseline	6 mo	Baseline	6 mo	Group	Time	Group × time
BMC_{TOT} (mg/mm)	429 (68)	426 (67)	419 (66)	417 (63)	0.543	0.238	0.705
$vBMD_{TOT}$ (mg/cm^3)	357 (39)	358 (40)	351 (53)	351 (53)	0.551	0.582	0.539
CSA_{TOT} (mm^2)	1204 (139)	1192 (130)	1204 (156)	1200 (143)	0.903	0.185	0.548
$vBMD_{TRAB}$ (mg/cm^3)	311 (34)	311 (34)	303 (44)	303 (44)	0.382	0.730	0.794
CSA_{TRAB} (mm^2)	1009 (135)	999 (133)	1001 (168)	995 (155)	0.862	0.141	0.726
BSI (g^2/cm^4)	1.55 (0.38)	1.54 (0.38)	1.49 (0.42)	1.49 (0.42)	0.556	0.511	0.995

Values are means (SD). The displayed p value denotes the main and interaction effects.

BMC_{TOT} = total BMC; $vBMD_{TOT}$ = total volumetric BMD; CSA_{TOT} = total cross-sectional area; $vBMD_{TRAB}$ = trabecular vBMD; BSI = bone strength index

Appendix D

Supplementary Table 2. Effects of strength and sprint training on polar mass distribution of the tibial shaft. Intention-to-treat analysis.

	Experimental group (n = 38)		Control group (n = 30)		ANOVA (p)		
BMC	Baseline	6 mo	Baseline	6 mo	Group	Time	Group × time
A	895 (130)	899 (128)	881 (157)	879 (153)	0.619	0.791	0.636
A-M	336 (65)	339 (66)	342 (63)	341 (63)	0.805	0.352	0.208
M	491 (110)	494 (108)	514 (99)	512 (99)	0.417	0.830	0.319
P-M	878 (141)	877 (135)	816 (161)	822 (159)	0.109	0.420	0.245
P	723 (142)	728 (145)	732 (148)	729 (145)	0.877	0.768	0.253
P-L	551 (99)	551 (96)	547 (86)	547 (88)	0.995	0.997	0.854
L	330 (64)	334 (64)	325 (68)	327 (70)	0.706	0.202	0.672
A-L	910 (168)	910 (891)	888 (133)	891 (144)	0.573	0.790	0.781

Values are means (SD). The displayed p value denotes the main and interaction effects. BMC values (mg/cm) are sum values of nine 5° sectors. (A = anterior, A-M = anteromedial, M = medial, P-M = posteromedial, P = posterior, P-L = posterolateral, L = lateral, A-L = anterolateral).

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II

REGULAR STRENGTH AND SPRINT TRAINING COUNTERACTS BONE AGING: A 10-YEAR FOLLOW-UP IN MALE MASTERS ATHLETES

by

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ORIGINAL ARTICLE

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Regular Strength and Sprint Training Counteracts Bone Aging: A 10-Year Follow-Up in Male Masters Athletes

Tuuli H Suominen,[1] Markku Alén,[2] Timo Törmäkangas,[1] Hans Degens,[3,4] Jörn Rittweger,[5,6] Ari Heinonen,[7] Harri Suominen,[7] and Marko T Korhonen[1]

[1]Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland
[2]Department of Medical Rehabilitation, Oulu University Hospital and Center for Life Course Health Research, University of Oulu, Oulu, Finland
[3]Department of Life Sciences, Musculoskeletal Science, and Sports Medicine Research Centre, Manchester Metropolitan University, Manchester, UK
[4]Institute of Sport Science and Innovations, Lithuanian Sports University, Kaunas, Lithuania
[5]Institute of Aerospace Medicine, German Aerospace Center (DLR), Cologne, Germany
[6]Department of Pediatrics and Adolescent Medicine, University of Cologne, Cologne, Germany
[7]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

ABSTRACT

Cross-sectional and interventional studies suggest that high-intensity strength and impact-type training provide a powerful osteogenic stimulus even in old age. However, longitudinal evidence on the ability of high-intensity training to attenuate age-related bone deterioration is currently lacking. This follow-up study assessed the role of continued strength and sprint training on bone aging in 40- to 85-year-old male sprinters ($n = 69$) with a long-term training background. Peripheral quantitative computed tomography (pQCT)-derived bone structural, strength, and densitometric parameters of the distal tibia and tibia midshaft were assessed at baseline and 10 years later. The groups of well-trained (actively competing, sprint training including strength training ≥2 times/week; $n = 36$) and less-trained (<2 times/week, no strength training, switched to endurance training; $n = 33$) athletes were formed according to self-reports at follow-up. Longitudinal changes in bone traits in the two groups were examined using linear mixed models. Over the 10-year period, group-by-time interactions were found for distal tibia total bone mineral content (BMC), trabecular volumetric bone mineral density (vBMD), and compressive strength index, and for mid-tibia cortical cross-sectional area, medullary area, total BMC, and BMC at the anterior and posterior sites (polar mass distribution analysis) ($p < 0.05$). These interactions reflected maintained (distal tibia) or improved (mid-tibia) bone properties in the well-trained and decreased bone properties in the less-trained athletes over the 10-year period. Depending on the bone variable, the difference in change in favor of the well-trained group ranged from 2% to 5%. The greatest differences were found in distal tibia trabecular vBMD and mid-tibia posterior BMC, which remained significant ($p < 0.05$) after adjustment for multiple testing. In conclusion, our longitudinal findings indicate that continued strength and sprint training is associated with maintained or even improved tibial properties in middle-aged and older male sprint athletes, suggesting that regular, intensive exercise counteracts bone aging. © 2021 The Authors. *JBMR Plus* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research.

KEY WORDS: AGING; BONE pQCT; EXERCISE; HIGH-IMPACT TRAINING; LONGITUDINAL STUDIES

Introduction

Although the ability of bone to adapt to physical exercise is most marked during youth, bone also retains some of its plasticity in later decades of life. However, participation in vigorous bone-loading exercise typically decreases with aging,[1] and reduced physical activity levels in old age likely contribute to the age-related loss of bone mass. Middle-aged and older masters athletes, although comprising only a small proportion of their cohort, provide a valuable model to study age-related changes in bone in the presence of regular high-intensity loading.[2] According to previous investigations, sprint training combining

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Address correspondence to: Tuuli H Suominen, MSc, Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, PO Box 35, 40014 Jyväskylä, Finland. E-mail: tuuli.suominen@jyu.fi
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running and supplementary jumping and strength exercises may provide the most powerful osteogenic training stimulus for the maintenance of bone mass and structural integrity with age, at least in the lower body skeleton.[3–12]

The tibia has been the focus of many exercise studies. Using peripheral quantitative computed tomography (pQCT), we and others have observed that in middle-aged and older masters sprint athletes, the indicators of bone strength of the distal and mid-shaft regions of the tibia are above average, yet they nevertheless show an age-related decline.[8,11] These cross-sectional studies may not, however, accurately indicate the longitudinal effects of aging and training on bone. In a previous randomized controlled trial with masters sprinters, we found that by combining intensive strength exercises with sport-specific sprint training, it is possible to improve mid-tibia structure and strength by 2% to 3% even after a rather short training period (20 weeks).[13] In addition, some studies have found significant changes in bone characteristics in response to high-intensity strength and impact training in nonathletic older adults with low bone mass.[14] Together, these studies suggest that the adaptability of bone to high-intensity exercise is likely maintained during aging. The osteogenic adaptations in our previous study, as in other exercise trials in older people in general,[14–19] were modest. However, if intense strength and impact training is maintained on a regular basis from midlife to late adulthood, it could attenuate the aging-related deterioration of bone structure and strength to ultimately reduce the risk of osteopenia and osteoporosis.

The present study expands our previous cross-sectional and experimental findings by providing long-term follow-up data on the same study population. The purpose of the study was to examine 10-year changes in pQCT-derived bone structural, strength, and densitometric parameters of the distal tibia and tibial midshaft in 40- to 85-year-old male masters sprinters and, most importantly, to assess the role of continued sport-specific sprint and strength training on the changes in bone traits. Owing to the wide age range of the participants, the results are also shown separately for the two age groups (40 to 64 and 65 to 85 years). An exploratory objective was to compare the changes in bone traits between cross-sectional estimates and longitudinal analyses.

Materials and Methods

Design and participants

This 10-year follow-up study was part of a larger research program investigating the effects of age and long-term sprint training on musculoskeletal characteristics and neuromuscular function among male masters athletes (ISRCTN17271498).[11,13,20] The recruitment procedure and study design have been described in detail earlier.[11,13] Briefly, 83 male masters sprinters (aged 40 to 85 years) with a long-term training background and success in international or national masters sprint events participated in the baseline measurements. To be eligible for the study, the athletes had to continue systematic training and competing in sprint events. Exclusion criteria included medications affecting bone metabolism.

Ten years later, the participants were recontacted by telephone and invited to participate in the follow-up study. Sixty-nine (83%) of the original 83 participants expressed willingness to continue in the study. Of the remaining participants, 6 had died, 3 could not be located, and 5 declined to participate because of poor health ($n = 4$) or lack of interest ($n = 1$). The main follow-up measurements were carried out at the same time of year (November to December) as at baseline. However, 15 participants were unable to attend this study visit. Their pQCT data were later obtained as part of a bone examination carried out in the same laboratory during the World Masters Indoor Championships held in Jyväskylä in April of the same year. All participants provided a written informed consent before participation in the study. The study was approved by the ethical committees of the University of Jyväskylä and the Central Finland Health Care District and conformed with the principles of the Declaration of Helsinki.

Based on their training and competition status at the time of follow-up, the athletes were categorized into two groups: well-trained ($n = 36$) and less-trained ($n = 33$). The well-trained group comprised those who reported ongoing systematic strength and sprint training at least twice weekly during the preceding year, divided into indoor and outdoor seasons, and participation in international or national masters sprint events. The less-trained group comprised those who reported strength and sprint training less than twice weekly, did no strength training, had retired from sport activities, had switched to endurance-type training and competing in endurance events, or reported taking long-term training breaks toward the end of the 10-year follow-up. Training frequency (main inclusion criterion for the well-trained group) was assessed separately for different training modes (strength, sprint, and plyometric training) and had to include both strength and sprint/plyometric types of training. In addition, questions covering the whole 10-year follow-up period (timing and length of possible training breaks, possible changes in training habits, competition history) were utilized to confirm participants' training and competitive status. Training breaks were evaluated according to their assumed effect (length and proximity to follow-up measurements) on the bone results. Based on our previous randomized controlled trial (RCT) with the same study population,[13] where the exercise-induced adaptations were likely derived from increased and intensified strength training, we were especially interested in the associations between strength training and bone aging. Hence, strength training was mandatory for an athlete to be categorized as well-trained.

Peripheral quantitative computed tomography

pQCT (XCT-2000, Stratec Medizintechnik, Pforzheim, Germany) scans were obtained from the distal tibia and tibial midshaft of the dominant leg (the leg used for take-off in a one-footed jump) according to previously described methods.[11,21] The same scanner was used in all the baseline and follow-up measurements. During the study, a daily quality assessment was performed using a standard phantom provided by the manufacturer. The distal tibia was scanned at 5% and the tibial midshaft at 50% of the tibia length proximal to the distal end plate. Tibia length was defined as the distance between the lateral malleolus and the lateral knee joint cleft. A single (2-mm) axial slice with a pixel size of 0.8 × 0.8 mm, typical tube voltage of 46 kV, tube current of 0.3 mA, and scan speed of 20 mm/s was obtained. The cross-sectional images were analyzed with the Geanie software program (version 2.1, Commit Ltd, Espoo, Finland). To determine the outer bone border, the segmentation threshold was set at 169 mg/cm^3 for the distal tibia and at 280 mg/cm^3 for the mid-tibia. Separation of subcortical/trabecular and cortical bone was performed using an automatic contour detection algorithm

(K-mode). At the distal site, bone marrow was included in the analyses, whereas at the midshaft site, bone marrow was excluded by applying a threshold of 100 mg/cm^3.

Total bone mineral content (BMC_{TOT}, mg/mm), trabecular volumetric BMD ($vBMD_{TRAB}$, mg/cm^3), total cross-sectional area (CSA_{TOT}, mm^2), and compressive bone strength index (BSI_{COMP}, g^2/cm^4 = $vBMD_{TOT}^2 \times CSA_{TOT}$)[22] were analyzed for the distal tibia. At the midshaft site, BMC_{TOT}, cortical vBMD ($vBMD_{CO}$), CSA_{TOT} (including bone marrow), cortical CSA (CSA_{CO}), medullary CSA ($CSA_M = CSA_{TOT}$-CSA_{CO}, including subcortical and medullary CSA), and density-weighted moments of inertia (I_{max} and I_{min}, mg*cm), reflecting the bone's resistance to bending in the direction of the greatest and smallest flexural rigidity, were determined. In addition, BMC was further analyzed as the polar distribution of bone mineral mass around its center, using 5° steps that were subsequently averaged into eight 45° sectors: anterior (A), anteromedial (A-M), medial (M), posteromedial (P-M), posterior (P), posterolateral (P-L), lateral (L), and anterolateral (A-L). The root mean square coefficient of variation (CV_{RMS}) for BMD, structure and strength index measurements in our laboratory ranges from 0.4 to 1.6%.[23]

Muscle CSA (mm^2) at the 50% site was analyzed by manually drawing along the outer boundary of the calf and applying thresholds of 11 and 280 mg/cm^3 to exclude fat and bone.

Anthropometry, health, training, and sprint performance

At baseline and at follow-up, the same methods were used to collect anthropometric, health, training, and sprint performance characteristics. Body height and mass were measured using a standard height gauge and a digital scale. Lean body mass (LBM) was assessed with a bioimpedance device (Spectrum II, RJL Systems, Detroit, MI, USA). Training status, health history, and current health of the athletes were assessed with a questionnaire and confirmed in a short interview and clinical examination. The questionnaire included detailed questions about current (during the preceding year, divided into indoor and outdoor seasons) and former training, competition performance, and injuries or diseases hindering physical training. At follow-up, the questionnaire also included items on long-term training breaks or significant decreases in the volume of strength and sprint training during the 10-year follow-up period. This data were utilized in the group allocation and are not reported in detail in this article. The health questionnaire included items on chronic diseases, medical operations, use of medical drugs and hormones, and smoking history. A 60-m sprint time on an indoor synthetic track with spiked shoes was obtained using double-beam photocell gates (starting line 0.7 m behind the first photocell gates). Own standing start without commands was used.

Statistical analysis

Data are presented as mean values and standard deviations (SD) or 95% confidence intervals (CI) and additionally with CIs with alpha-level adjustment for 19 simultaneous tests for the main analysis. Baseline physical and training characteristics of the well-trained and less-trained athletes were compared by independent samples *t* test. The association of continued strength and sprint training with longitudinal changes in bone outcomes was assessed based on an interaction term (group × time) in linear mixed models adjusted for age. The longitudinal changes in physical and training characteristics in the two groups were also examined using a similar approach. Neither the original randomization group nor anthropometric data were included in the bone outcome analyses because these were not associated with training status or the longitudinal changes in bone. One athlete was removed from the mid-tibia analysis owing to movement artifact. Figures show individual and mean changes in the bone variables standardized with respect to their baseline measurement. Owing to the wide age range of the participants and possible differences in their training habits and/or responses, these changes were also calculated, as a sensitivity analysis, separately for two age groups aged 40 to 64 years (well-trained, $n = 21$; less-trained, $n = 18$) and 65 to 85 years ($n = 15$ and 15, respectively). The division into these age groups is based on our previous RCT[13] with the same cohort. Finally, as an additional supplementary illustration, we compared the changes at follow-up with the changes predicted from the cross-sectional data. The point estimates and 95% CIs of the longitudinal 10-year changes within individuals in bone traits were compared with the 10-year predicted changes in estimated marginal means (% per decade) computed from cross-sectional linear models with baseline bone traits as the dependent variable and continuous age as the predictor. Descriptive analyses were performed using SPSS 24.0 software (IBM Corp., Armonk, NY, USA) and the parameters of the linear mixed models were estimated and model-derived statistics computed with custom scripts utilizing the nlme (version 3.1-148) and emmeans packages (version 1.5.1) in R version 3.5.1 (R core team, Vienna, Austria).

The significance level was set at 5%. For the descriptive analysis, we report nominal *p* values and for the mixed analyses, both nominal and multiplicity-adjusted *p* values and 95% CIs. Conducting several tests on the same data set increases the risk of false positives, whereas the conservative methods used to correct for multiple correlated tests tend to reject true positives along with false ones. For this reason, we utilized a correction procedure introduced by Cheverud[24] that replaces the observed number of independent tests with their effective number. The effective number of tests is based on the independent number of sources of variability approximated by the eigenvalues of the outcome correlation matrix. Because the main tests for our analysis focus on changes over time (interactions), we used the correlation matrix of the follow-up differences (follow-up baseline) in computing the number of effective comparisons, M_{eff}. We adopted the convention introduced by Nyholt[25] and call M_{eff} the number of effective comparisons and the significance level $1 - (1 - \alpha)^{1/Meff}$ the M_{eff}-Šidák-corrected significance level. The approximate number of tests for the 19 outcomes was 16, yielding a M_{eff}-Šidák-adjusted alpha of 0.00317. Standard errors for CIs for mean changes were computed based on the multiparameter version of the delta method (see, eg, Raykov and colleagues[26]).

Results

Physical and training characteristics

The baseline and 10-year follow-up characteristics of the athletes are shown in Table 1. {TBL 1} Mean follow-up time was 9.8 ± 0.2 years. No differences between the groups of well-trained and less-trained athletes were observed in baseline physical and training characteristics except in the frequency of strength training, which was significantly higher in the well-trained group ($p = 0.002$). Equally, no between-group differences over time were observed in these outcomes. Mean training years at baseline were 31.5 (SD 16.0) for the well-trained

Table 1. Baseline and Follow-Up Physical, Training, and Bone Characteristics of Well-Trained and Less-Trained Athletes

	Baseline		10 years	
	Well-trained ($n = 36$)	Less-trained ($n = 33$)	Well-trained ($n = 36$)	Less-trained ($n = 33$)
Age (years)	60.8 (9.5)	60.5 (12.7)	70.6 (9.4)	70.4 (12.7)
Height (cm)	174 (6)	176 (6)	173 (6)	175 (7)
Mass (kg)	73.6 (7.0)	73.4 (7.8)	73.2 (7.9)	74.5 (8.8)
Lean body mass (kg)	63.2 (6.4)	62.9 (5.8)	62.1 (5.9)[a]	61.5 (6.5)[b]
Muscle CSA (mm^2)	6763 (852)	6858 (1129)	6764 (923)	6893 (1265)
60-m sprint time (s)	8.36 (0.58)[c]	8.63 (0.94)	9.32 (1.09)[b]	9.94 (2.45)[d]
Training frequency (sessions/wk)	4.5 (1.2)	4.3 (1.3)	4.2 (1.3)	3.3 (1.5)
Running and plyometrics (times/wk)	3.4 (1.5)	2.9 (1.6)[e]	2.1 (0.6)	0.8 (1.3)
Strength training (times/wk)	1.1 (0.7)	0.6 (0.6)[e]	1.4 (0.7)	0.7 (1.1)
Tibia 5%				
BMC_{TOT} (mg/mm)	427 (64)	420 (70)	425 (65)	405 (73)
CSA_{TOT} (mm^2)	1195 (139)	1215 (172)	1192 (132)	1208 (175)
$vBMD_{TRAB}$ (mg/cm^3)	315 (39)	300 (38)	314 (41)	291 (43)
BSI_{COMP} (g^2/cm^4)	1.55 (0.39)	1.48 (0.39)	1.54 (0.41)	1.39 (0.40)
Tibia 50%				
CSA_{TOT} (mm^2)	592 (60)	599 (71)	598 (59)	605 (73)[e]
CSA_{CO} (mm^2)	416 (50)	416 (46)	420 (48)	410 (51)[e]
CSA_M (mm^2)	177 (43)	183 (44)	178 (47)	195 (45)[e]
I_{max} (mg*cm)	4920 (1004)	5013 (1281)	5080 (1012)	5072 (1291)[e]
I_{min} (mg*cm)	1783 (384)	1849 (430)	1788 (367)	1862 (459)[e]
BMC_{TOT} (mg/mm)	508 (58)	511 (58)	513 (58)	506 (61)[e]
$vBMD_{CO}$ (mg/cm^3)	1095 (24)	1096 (26)	1093 (34)	1097 (30)[e]

Muscle CSA = muscle cross-sectional area; BMC_{TOT} = total bone mineral content; CSA_{TOT} = total CSA; $vBMD_{TRAB}$ = trabecular volumetric bone mineral density; BSI_{COMP} = compressive bone strength index; CSA_{CO} = cortical CSA; CSA_M = medullary CSA; I_{max}, I_{min} = density-weighted maximal and minimal moments of inertia; $vBMD_{CO}$ = cortical vBMD.

Values are means (SD). Note: 15 participants were unable to attend the main follow-up measurements when lean body mass and sprint performance were assessed.

[a] $n = 31$.
[b] $n = 25$.
[c] $n = 34$.
[d] $n = 16$.
[e] $n = 32$.

and 30.9 (16.4) for the less-trained ($p = 0.897$) athletes. At 10 years, only a subsample of the participants completed the sprint performance and LBM measurements, as these assessments were conducted only during the main follow-up measurements, which 15 participants were unable to attend. In addition, 13 participants did not participate in the sprint performance testing because of a musculoskeletal disorder ($n = 8$) or a chronic medical condition ($n = 5$).

None of the participants reported taking any medications that affected bone metabolism. Three participants in the well-trained and 3 in the less-trained group presented with prostate cancer. All participants were free of other diseases that could affect bone, such as rheumatoid arthritis, celiac disease, or colitis ulcerosa. One current smoker was found in the well-trained group and 6 former smokers in each group (12 former smokers in total).

Bone traits

No differences were observed in baseline bone characteristics between the well-trained and less-trained (Table 1) except for distal tibia BMC_{TOT} and $vBMD_{TRAB}$, which were significantly higher in the 40- to 64-year-old well-trained than less-trained group (Supplemental Table S1).

The associations of continued strength and sprint training with changes in the distal tibia bone traits are shown in Table 2, {TBL 2} Fig. 1, {FIG1} and Supplemental Fig. S1. At the distal tibia site, a significant group × time interaction was found for $vBMD_{TRAB}$ ($p = 0.003$, raw value). $vBMD_{TRAB}$ was maintained in the well-trained and decreased (−3.2%) in the less-trained athletes over the 10-year period (Fig. 1). At follow-up, the mean difference in the change in $vBMD_{TRAB}$ in favor of the well-trained was 2.8% (Fig. 1). A similar pattern was found for BMC_{TOT} and BSI_{COMP}. In the well-trained group, BMC_{TOT} and BSI_{COMP} were maintained, whereas in the less-trained group they decreased by 3.5% and 5.9%, respectively (Fig. 1). The corresponding differences in change in favor of the well-trained were 3.1% and 5.2%. After adjustment for multiple testing, the difference in $vBMD_{TRAB}$ between the groups remained significant.

The associations of continued strength and sprint training with changes in the tibial mid-shaft bone traits are shown in Tables 3 and 4, {TBL 3}{TBL 4} Figs. 1 and 2, {FIG2} and Supplemental Figs. S1 and S2. A significant group × time interaction was found for CSA_{CO} ($p = 0.006$, raw value) and BMC_{TOT} ($p = 0.019$, raw value). This reflected the increase in CSA_{CO} (+1.1%) and BMC_{TOT} (+0.8%) in the well-trained and the decrease in both parameters (−1.4% and −0.9%, respectively) in the less-trained athletes over the 10-year period (Fig. 1). A significant group × time interaction found for CSA_M ($p = 0.006$, raw value) was reflected in the maintained CSA_M in the well-trained and increased CSA_M (+4.9%) in the less-trained athletes over

Table 2. Associations of Continued Strength and Sprint Training With Changes in Distal Tibia Bone Traits of the Masters Athletes

				Multiple testing					
				Unadjusted			Adjusted		
	Group	BL	10-year change	95% CI		Group × time	95% CI		Group × time
BMC_{TOT} (mg/mm)	WT	427	−1.7	−9.1	5.7	0.019	−13.8	10.5	0.267
	LT	420	−14.5	−22.3	−6.8		−27.3	−1.8	
CSA_{TOT} (mm^2)	WT	1195	−2.8	−17.1	11.5	0.743	−26.3	20.8	1.000
	LT	1209	−6.2	−21.1	8.8		−30.8	18.4	
$vBMD_{TRAB}$ (mg/cm^3)	WT	315	−1.5	−5.2	2.2	0.003	−7.5	4.6	0.048
	LT	300	−9.7	−13.6	−5.9		−16.0	−3.4	
BSI_{COMP} (g^2/cm^4)	WT	1.55	−0.01	−0.05	0.03	0.013	−0.08	0.06	0.193
	LT	1.47	−0.09	−0.13	−0.04		−0.16	−0.02	

BL = baseline; CI = confidence interval; WT = well-trained (n = 36); LT = less-trained (n = 33); BMC_{TOT} = total bone mineral content; CSA_{TOT} = total cross-sectional area; $vBMD_{TRAB}$ = trabecular volumetric bone mineral density; BSI_{COMP} = compressive bone strength index.
Values are estimated means. 95% CI for absolute change.

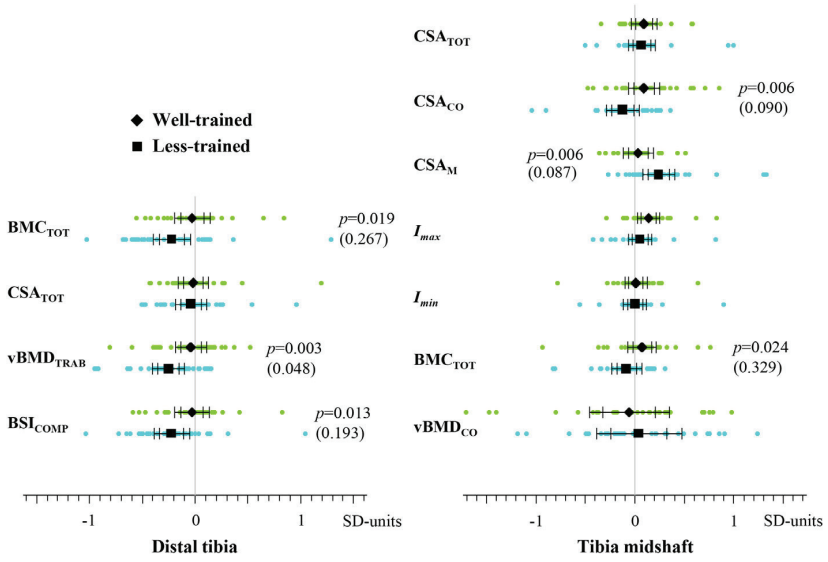

Fig. 1. Ten-year changes in distal tibia (*A*) and tibia midshaft (*B*) in well-trained and less-trained athletes. Outcomes were standardized with respect to their baseline values. Individual data points, group means, and 95% confidence intervals (CIs) for unadjusted (narrower CIs) and M_{eff}-Sidák multiple test-corrected (wider CIs) analyses are presented. The displayed p values denote the unadjusted group × time interaction effect if $p < 0.05$. Multiplicity adjusted p values are shown in parentheses. Cases in the well-trained group with $vBMD_{CO} = -3.36$ and 2.54 were cropped from the figure on the right-hand side.

the follow-up. The mean difference in change in favor of the well-trained was 2.5% for CSA_{CO}, 1.8% for BMC_{TOT}, and 4.2% for CSA_M (Fig. 1). After adjustment for multiple testing, the interactions were no longer significant, although CSA_{CO} and CSA_M showed an increasing trend in the well-trained compared with less-trained athletes ($p = 0.090$ and $p = 0.087$, respectively).

The polar mass distribution of the tibial shaft showed a significant group × time interaction at the anterior and the posterior sites (Table 4 and Fig. 2). This was reflected in a site-specific increase in BMC in the well-trained and no change in the less-trained athletes at follow-up. In the well-trained compared with less-trained athletes, BMC_A increased by 3.5% and BMC_P by 5.1% (Fig. 2). After adjustment for multiple testing, BMC_P remained significant.

The mean changes in bone traits of the well-trained and less-trained athletes across the age groups are shown in Supplemental Figs. S1 and S2. The significant interactions (group × time, $p < 0.05$, raw values) and differences in changes in the bone outcomes observed in the main analyses (Figs. 1 and 2) were manifested in the age groups as follows. In the group aged 40 to 64 years, the mean difference in change in distal tibia bone traits in the well-trained compared with less-trained athletes was 3.2% for BMC_{TOT}, 3.5% for $vBMD_{TRAB}$, and 5.9% for BSI_{COMP}. These manifested as maintained bone properties in the well-trained and decreased bone properties in the less-trained athletes over the

Table 3. Associations of Continued Strength and Sprint Training With Changes in Tibial Mid-Shaft Bone Traits of the Masters Athletes

				Multiple testing					
				Unadjusted			Adjusted		
	Group	BL	10-year change	95% CI		Group × time	95% CI		Group × time
CSA_{TOT} (mm^2)	WT	518	6.0	0.6	11.5	0.724	−3.0	15.0	1.000
	LT	524	4.6	−1.2	10.4		−4.9	14.1	
CSA_{CO} (mm^2)	WT	416	4.5	−0.4	9.5	0.006	−3.7	12.7	0.090
	LT	416	−5.8	−11.1	−0.6		−14.5	2.9	
CSA_{M} (mm^2)	WT	205	1.5	−2.8	5.8	0.006	−5.6	8.5	0.087
	LT	212	10.4	5.9	15.0		3.0	17.9	
I_{max} (mg*cm)	WT	4918	161	76	245	0.109	22	299	0.845
	LT	5014	61	−28	150		−86	208	
I_{min} (mg*cm)	WT	1782	5.0	−24	34	0.852	−43	53	1.000
	LT	1861	1.0	−30	32		−50	52	
BMC_{TOT} (mg/mm)	WT	508	4.3	−1.1	9.6	0.024	−4.6	13.1	0.329
	LT	511	−4.8	−10.5	0.9		−14.2	4.6	
$vBMD_{CO}$ (mg/cm^3)	WT	1095	−1.4	−8.0	5.2	0.617	−12.2	9.5	1.000
	LT	1096	1.0	−6.0	8.0		−10.5	12.5	

BL = baseline; CI = confidence interval; WT = well-trained ($n = 36$); LT = less-trained ($n = 32$); CSA_{TOT} = total cross-sectional area; CSA_{CO} = cortical CSA; CSA_{M} = medullary CSA; I_{max}, I_{min} = density-weighted maximal and minimal and moments of inertia; BMC_{TOT} = total bone mineral content; $vBMD_{CO}$ = cortical volumetric bone mineral density.

Values are estimated means. 95% CI for absolute change.

Table 4. Associations of Continued Strength and Sprint Training With Changes in Polar Mass Distribution of the Tibial Shaft of the Masters Athletes

				Multiple testing					
				Unadjusted			Adjusted		
BMC	Group	BL	10-year change	95% CI		Group × time	95% CI		Group × time
A	WT	913	29.4	11.5	47.3	0.017	−0.03	58.8	0.241
	LT	894	−2.6	−21.6	16.4		−33.8	28.6	
A-M	WT	344	1.9	−4.4	8.1	0.077	−8.4	12.1	0.726
	LT	349	−6.4	−13.0	0.3		−17.3	4.6	
M	WT	476	−2.3	−12.1	7.5	0.419	−18.4	13.8	1.000
	LT	495	−8.1	−18.5	2.3		−25.2	9.0	
P-M	WT	859	1.6	−12.8	15.9	0.283	−22.0	25.2	0.995
	LT	856	−9.8	−25.0	5.4		−34.8	15.3	
P	WT	727	25.8	11.9	39.7	<0.001	2.9	48.6	0.008
	LT	740	−11.4	−26.1	3.3		−35.6	15.3	
P-L	WT	563	−2.1	−12.2	7.9	0.678	−18.6	14.4	1.000
	LT	554	−5.2	−15.9	5.4		−22.7	12.3	
L	WT	321	−6.5	−13.9	0.8	0.590	−18.6	5.6	1.000
	LT	327	−9.4	−17.2	−1.6		−22.2	3.4	
A-L	WT	877	−5.2	−26.9	16.4	0.518	−40.9	30.4	1.000
	LT	892	5.0	−17.9	28.0		−32.7	42.8	

BMC = bone mineral content; BL = baseline; CI = confidence interval; WT = well-trained ($n = 36$); LT = less-trained ($n = 32$); A = anterior; A-M = anteromedial; M = medial; P-M = posteromedial; P = posterior; P-L = posterolateral; L = lateral; A-L = anterolateral.

Values are estimated means. 95% CI for absolute change. BMC – values (mg/cm) are sum values of nine 5° sectors.

10-year follow-up period (Supplemental Fig. S1). In the group aged 65 to 85 years, the 4.1% difference in change in mid-tibia CSA_{CO} was reflected as maintained CSA_{CO} in the well-trained and decreased CSA_{CO} in the less-trained athletes, whereas the 5.3% difference in change in CSA_{M} comprised no change in the well-trained and an increase in the less-trained athletes (Supplemental Fig. S1). Among the 40- to 64-year-olds, BMC_{A} and BMC_{P} increased over time in the well-trained group and were maintained in the less-trained group (Supplemental Fig. S2). The difference in change in favor of the well-trained was 5.2% in BMC_{A} and 3.9% in BMC_{P}. Among the 65- to 85-year-olds, the difference in change in BMC_{P} at follow-up was 6.2%, comprising an increase in the well-trained and a decrease in less-trained athletes over the follow-up (Supplemental Fig. S2).

In general, the longitudinal changes in bone traits did not follow the cross-sectional trends predicted by the athletes' baseline values (estimated cross-sectional changes in comparison to longitudinal changes; Supplemental Table S2). For the distal tibia

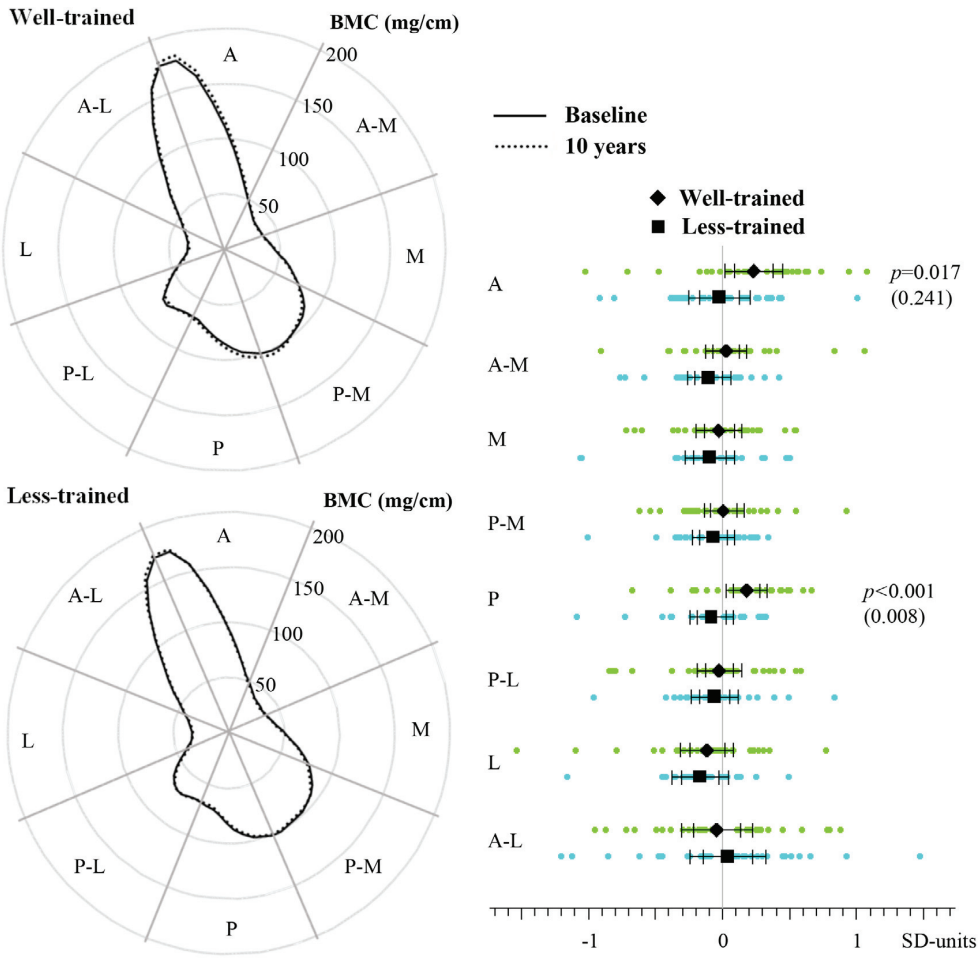

Fig. 2. (*A*) Mean polar mass distribution curves for the well-trained (upper panel) and less-trained (lower panel) athletes at baseline and at the 10-year follow-up indicating the angular distribution of bone mineral mass around the center of mass in 5° steps that were subsequently averaged into eight 45° sectors. A = anterior; A-M = anteromedial; M = medial; P-M = posteromedial; P = posterior; P-L = posterolateral; L = lateral; A-L = anterolateral. (B) Ten-year changes in polar mass distribution of the tibial shaft in well-trained and less-trained. Outcomes were standardized with respect to their baseline values. Individual data points, group means, and 95% confidence intervals (CIs) for unadjusted (narrower CIs) and M_{eff}-Sidák multiple test-corrected (wider CIs) analyses are presented. The displayed *p* values denote the unadjusted group × time interaction effect if $p < 0.05$. Multiplicity adjusted *p* values shown in parentheses.

site, the mean change per decade predicted by the cross-sectional analysis was −3.4% (range −7.2% [BSI_{COMP}] to 0.5% [CSA_{TOT}]) for all participants compared with the −1.8% (range −3.1% [BSI_{COMP}] to −0.4% [CSA_{TOT}]) found by the longitudinal analysis. For the midshaft site, the corresponding changes were −3.4% (range −6.5% [I_{max}] to −0.3% [$vBMD_{CO}$]) and 0.5% (range −0.1% [CSA_{CO}] to 2.3% [I_{max}]).

Discussion

In this 10-year follow-up study of middle-aged and older male sprint athletes, we found that regularly continued strength and sprint training was associated with maintained distal tibia trabecular density and with improved tibial midshaft bone mass at the posterior site (polar mass distribution analysis). In addition, a trend was found for an increased mid-tibial cortical area in the well-trained compared with less-trained athletes, whereas the medullary area was maintained in the well-trained and increased in the less-trained athletes over the follow-up. In the unadjusted analyses, significant group differences were found in distal tibia trabecular density, bone mass, and compressive strength, and in mid-tibial cortical area, medullary area, bone mass, and BMC in the anteroposterior direction.

Longitudinal analysis of bone traits in masters sprint/power athletes has been limited to a single investigation[27] and no previous data are available on the importance of sustained sport-specific training on bone changes with aging. In line with our

present findings, a recent 4-year longitudinal study by Ireland and colleagues[27] found greater maintenance of distal (4%) and mid-tibial (66%) BMC in masters power (sprinting and jumping) than endurance athletes aged 37 to 85 years. At the distal site, the differences resulted from better maintenance of trabecular BMD, whereas at mid-tibia, they were explained by the maintenance of cortical thickness and cortical BMD.[27] Longitudinal studies conducted on middle-aged and older masters long-distance runners have shown maintained areal BMD at the hip and spine[28,29] but have not examined changes in bone structure, strength, and volumetric density.

In the present study, as in previous cross-sectional[7,9,11] and experimental studies[13] on masters athletes and a twin study,[21] the adaptations in cortical bone at the mid-tibia site were mostly structural, whereas in the distal tibia, maintained bone strength was related to densitometric adaptations in trabecular bone. In our previous RCT with the same study population,[13] we did not find exercise-induced adaptations in the distal tibia, which was not surprising given the brevity of the intervention in these highly trained participants. In the present 10-year follow-up study, in accordance with recent findings on the positive effects of high-intensity strength and impact training on nonathletic middle-aged and older men with low bone mass,[14] distal tibia BMC_{TOT}, trabecular vBMD, and BSI_{COMP} were maintained in the well-trained and decreased in the less-trained athletes. The association with trabecular density remained significant even after adjusting for multiple testing. Overall, the more pronounced densitometric changes found in the 40- to 64-year-old group of athletes could be explained by the higher vertical compression forces exerted during impact-type training. It is well known that normal aging processes impose limitations on training tolerance (eg, reduced recovery) and that many masters competitors are unable to maintain their absolute training intensity and volume as they enter old age.[30–34] Even in the well-trained group, absolute training intensities were likely lower in the older than younger athletes, although the relative training load might have been similar.

The adaptations at the mid-tibia site were manifested as increased direction-specific bone mass, which reflects the site-specific nature of the observed increase in BMC_{TOT} and cortical area. In the well-trained athletes, bone mass and cortical CSA increased, while in the less-trained they declined. These improvements in bone mass and structure without increases in vBMD are in line with our previous RCT on masters athletes[13] and with other exercise trials on aging nonathletes.[35–37] The number of trials focusing on bone structure and strength among aging people is, however, limited, and studies have reported conflicting results,[38,39] possibly owing to short training periods and/or less-intensive training regimens. In the present long-term follow-up, our sample included athletes who were able and competitively motivated to train at high intensities, enabling us to examine the long-term association of training on bone aging. In contrast to the changes at the distal site, we observed more pronounced structural improvements at the mid-tibia site in the 65- to 85-year-olds, indicating that the bending (and torsional) loading derived from strength and plyometric training may be an effective way to preserve bone even in old age. Moreover, the beneficial effect of such training on muscles (muscle mass, strength, and power) may further improve bone not only through increased loading from muscle contraction but possibly also through diverse (mechanical and non-mechanical) muscle-bone interactions.[40,41] In line with longitudinal findings on masters power and endurance athletes,[27] muscle CSA measured at the mid-tibia site did not correlate with training status or changes in bone. We suggest that the calf muscles may not adequately reflect the differences in the effects of training on the tibia, which is more likely affected by muscle pull from the knee extensors than by the muscles located at the tibial site.[42] The knee flexors, which are highly important muscles in sprint performance, may also affect the tibia.[43]

According to the bone mass distribution of the midshaft, the well-trained group showed increased bone mass in the A-P direction, as also found in previous cross-sectional athlete[11,44,45] and twin studies[21] and in an RCT combining hormone-replacement therapy with high-impact training.[46] In those studies, the site-specific increase in bone mass was seen as an increase in direction-specific bending strength at the maximum axis (I_{max}). The increase in I_{max} probably relates to posterior bending, which is the habitual loading pattern during sprint training and other weight-bearing activities.[47] In the present study, in accordance with recent longitudinal findings on masters athletes by Ireland and colleagues,[27] I_{max} increased in both groups, although the well-trained athletes showed a trend to a greater increase. The overall increase in I_{max} and I_{min} may also reflect age-related endocortical resorption and compensatory periosteal apposition, ie, shift of the cortex further from the neutral axis.[48] This is also supported by the overall increase in total bone area observed in the present study. The increases in I_{max} and CSA_{TOT} were less evident in the older less-trained group of athletes, which further supports the benefits of regular training in old age.

The longitudinal changes in bone traits in the present study were relatively small. Because we did not include sedentary controls, direct comparisons with non-exercisers cannot be made. However, previous longitudinal studies on non-exercising older men are available.[49,50] Although not fully comparable with our results because of the different imaging method (high-resolution [HR]-pQCT) used, Burt and colleagues[49] reported an annual decline of 0.3% to 1.1% in distal tibia density in men older than age 50 years. Similarly, by combining cross-sectional and longitudinal data, Lauretani and colleagues[50] observed significant lifetime decreases (approximately −20% between ages 20 and 100 years) in distal tibia total and trabecular vBMD measured by pQCT. In the present study, the mean decrease per decade in distal tibia $vBMD_{TRAB}$ was 0.5% in the well-trained and 3.5% in the less-trained athletes.

At the mid-tibia site, Lauretani and colleagues[50] reported slight age-related increases in cortical and total CSA, particularly before midlife. However, estimated bending strength declined over the life span. Continuous periosteal apposition was reported, especially during young adulthood and midlife. In the present study, no significant increase in total CSA in the well-trained compared with less-trained athletes was found, whereas medullary area increased in the less-trained but remained unchanged in the well-trained athletes. Together, these observations suggest that exercise-induced adaptations were more likely to occur in the endocortical than periosteal surfaces, reflecting reduced endocortical bone loss in the well-trained athletes. This accords with an animal study by Birkhold and colleagues[51] suggesting that the mechanoresponsiveness of the endocortical surface is better preserved during aging than the periosteal surface. Overall, the age-related changes in the above-mentioned longitudinal studies were not linear, which is supported by the age-group differences observed in the present study. At the distal site, the densitometric properties were best preserved in the younger well-trained group, whereas at the mid-tibia site, the bone properties were maintained or even

improved in all athletes except those in the older less-trained group. Furthermore, in accordance with Lauretani and colleagues,[50] we found that the cross-sectional linear trends derived from the baseline data were poor predictors of the longitudinal changes in bone (Supplemental Table S2). The differences in the results suggest that even in a relatively homogeneous group, predictions based on age alone poorly generalize the longitudinal processes that relate to modifications in individuals' bone characteristics.

The main limitation of this study is its observational nature, which only allows the reporting of associations, not causal relationships. We cannot totally exclude the possible influence on bone of other factors, such as genetics or diseases. It is noteworthy that many aging athletes continue to train and compete despite sustaining mild sports injuries and having potentially progressive diseases. Health-related factors could, however, lead to an accelerated decline in bone strength, for example, by limiting the amount of systematic training. In the present sample, equal numbers of athletes in the well-trained and less-trained groups presented with prostate cancer, and their exclusion did not change the results. The athletes with cancer did not differ from the healthy athletes in their bone results or anthropometric or training characteristics. Moreover, review of the information on time of diagnosis and the treatment methods used also showed that the disease had no substantial effect on bone. Another potential limitation is that the group allocation into well-trained and less-trained athletes was based on self-reported physical activity levels. However, with an athlete population accustomed to keeping exercise diaries on a regular basis, the probability of recall bias is likely to be lower than average. Furthermore, in the group allocation, special emphasis was placed on strength training, which was already low in the less-trained group at baseline. However, as reported in the RCT,[13] the previous strength training of the athletes had focused on strength endurance exercises (higher repetitions with low-intensity loads) rather than the heavy and explosive exercises that were administered to all participants (experimental and control) along with the RCT. The original randomization grouping was not taken into account in the present analysis because it was not associated with 10-year training status or the longitudinal changes in bone. Given the lengthy time frame and the independently performed training program that was fully provided for the control participants after completion of the trial, the RCT is unlikely to affect the current results. The less-trained athletes were also highly active, and many were actively competing. We did, however, find that with specific intensive training, bone properties were better preserved, even in older participants. The present age group data are, however, exploratory, ie, hypothesis-generating rather than hypothesis-confirming. Given the considerable number of bone variables analyzed, the sample size was not sufficient for more fine-grained age group analyses. To describe the mechanisms behind the bone changes, multiple outcomes of interest were preferred instead of a single outcome. Moreover, to avoid issues related to multiple testing, the results are presented both in raw form and corrected for multiple testing.

This study presents novel findings on the adaptability of the aging male skeleton to exercise and the extent to which regular intensive training counteracts age-related changes in bone. The strengths of this study include the longitudinal design and the unique study population. As part of a larger research program including both cross-sectional and experimental study designs, the present sample was carefully selected to represent high-level competitive sprint athletes with years of habitual intensive training. Moreover, given the long-term follow-up, the retention rate was relatively high. A further strength of the study is the use of 3D imaging to detect changes in bone cross-sectional geometry and volumetric density, although a higher-resolution technology would have yielded even more detailed results. Furthermore, detailed mass distribution analysis has been reported in only a few earlier studies, and we are not aware of previous longitudinal data on masters athletes.

In conclusion, this longitudinal study suggests that regular strength and sprint training counteracts bone aging in middle-aged and older men. Continued intensive training may hinder bone deterioration among even the oldest athletes, but more research is needed to confirm this. The present longitudinal findings further support the adaptability of aging bone to physical exercise and highlight the importance of a regular, intensive training stimulus for maintaining bone health. Further longitudinal studies should address the effects of combined strength and sprint/impact training on age-related changes at the clinically important proximal femur site, also in female athletes and in sedentary aging people. Strength training and other high-intensity training have become increasingly popular among older people, and exercises targeted at improving muscle force–generating capacity are highly recommended at all ages.

Disclosures

All authors state that they have no conflicts of interest.

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Authors' roles: Study design: MK and HS. Study conduct: MK, HS, and MA. Data collection: TS, MA, HS, and MK. Data analysis: TS and TT. Data interpretation: TS, MA, AH, HS, and MK. Drafting manuscript: TS. Revising manuscript content: TS, MA, TT, AH, HD, JR, HS, and MK. Approving final version of manuscript: TS, MA, TT, AH, HD, JR, HS, and MK. TS and TT take responsibility for the integrity of the data analysis.

Author Contributions

Tuuli Suominen: Formal analysis; investigation; methodology; visualization; writing-original draft; writing-review & editing. **Markku Alen:** Investigation; writing-review & editing. **Timo Tormakangas:** Formal analysis; methodology; writing-review & editing. **Hans Degens:** Writing-review & editing. **Joern Rittweger:** Writing-review & editing. **Ari Heinonen:** Writing-review & editing. **Harri Suominen:** Conceptualization; funding acquisition; investigation; methodology; project administration; supervision; writing-review & editing. **Marko Korhonen:** Conceptualization; funding acquisition; investigation; methodology; project

administration; supervision; writing-original draft; writing-review & editing.

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III

EFFECTS OF A HOME-BASED PHYSICAL REHABILITATION PROGRAM ON TIBIAL BONE STRUCTURE, DENSITY, AND STRENGTH AFTER HIP FRACTURE: A SECONDARY ANALYSIS OF A RANDOMIZED CONTROLLED TRIAL

by

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ORIGINAL ARTICLE

Effects of a Home-Based Physical Rehabilitation Program on Tibial Bone Structure, Density, and Strength After Hip Fracture: A Secondary Analysis of a Randomized Controlled Trial

Tuuli H Suominen,[1] Johanna Edgren,[1] Anu Salpakoski,[2] Marja Arkela,[3] Mauri Kallinen,[3,4] Tomas Cervinka,[5] Timo Rantalainen,[1] Timo Törmäkangas,[1] Ari Heinonen,[6] and Sarianna Sipilä[1]

[1]Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland
[2]Rehabilitation Center Peurunka, Laukaa, Finland
[3]Department of Physical and Rehabilitation Medicine, Central Finland Central Hospital, Jyväskylä, Finland
[4]Department of Medical Rehabilitation, Oulu University Hospital and Center for Life Course Health Research, University of Oulu, Oulu, Finland
[5]Satakunta University of Applied Sciences, Pori, Finland
[6]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland

ABSTRACT

Weight-bearing physical activity may decrease or prevent bone deterioration after hip fracture. This study investigated the effects of a home-based physical rehabilitation program on tibial bone traits in older hip fracture patients. A population-based clinical sample of men and women operated for hip fracture (mean age 80 years, 78% women) was randomly assigned into an intervention ($n = 40$) and a standard care control group ($n = 41$) on average 10 weeks postfracture. The intervention group participated in a 12-month home-based rehabilitation intervention, including evaluation and modification of environmental hazards, guidance for safe walking, nonpharmacological pain management, motivational physical activity counseling, and a progressive, weight-bearing home exercise program comprising strengthening exercises for the lower legs, balance training, functional exercises, and stretching. All participants received standard care. Distal tibia (5% proximal to the distal end plate) compressive bone strength index (BSI; g^2/cm^4), total volumetric BMD ($vBMD_{TOT}$; mg/cm^3), and total area (CSA_{TOT}; mm^2), as well as midtibia (55%) strength–strain index (SSI; mm^3), cortical vBMD ($vBMD_{CO}$; mg/cm^3), and ratio of cortical to total area (CSA_{CO}/CSA_{TOT}) were assessed in both legs by pQCT at baseline and at 3, 6, and 12 months. The intervention had no effect (group × time) on either the distal or midtibial bone traits. At the distal site, BSI of both legs, $vBMD_{TOT}$ of the fractured side, and CSA_{TOT} of the nonfractured side decreased significantly over time in both groups 0.7% to 3.1% (12 months, $p < 0.05$). At the midshaft site, CSA_{CO}/CSA_{TOT} and SSI of both legs, and $vBMD_{CO}$ of the fractured leg, decreased significantly over time in both groups 1.1% to 1.9% (12 months, $p < 0.05$). Trabecular and cortical bone traits of the tibia on the fractured and the nonfractured side deteriorated throughout follow-up. The home-based physical rehabilitation intervention aimed at promoting mobility recovery was unable to prevent bone deterioration in older people after hip fracture. © 2019 The Authors. *JBMR Plus* published by Wiley Periodicals, Inc. on behalf of American Society for Bone and Mineral Research.

KEY WORDS: AGING; BONE QCT/MCT; CLINICAL TRIALS; EXERCISE; INJURY/FRACTURE HEALING

Introduction

The substantial and long-term decline in bone properties that occurs after hip fracture[1–5] markedly increases the risk for a second fracture.[6,7] In the contralateral hip, as measured by DXA, the loss of bone density, structure, and strength over the year after fracture far exceeds the decrements from normal aging, in both men and women.[1,3–5] Cross-sectional studies using peripheral 3D-imaging modalities have also revealed marked impairments in tibial properties on both the fractured and nonfractured sides.[2,8] These reductions were most evident in bone geometric properties[2,8] and correlated with hip BMD measured by DXA.[8] In our previous study,[2] with individuals on average 3.5 years post hip fracture, a considerable and persistent

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Address correspondence to: Sarianna Sipilä, Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, P.O. Box 35, 40014 Jyväskylä, Finland. E-mail: sarianna.sipila@jyu.fi
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side-to-side difference in geometric properties favoring the nonfractured leg was observed. Part of this bone loss was presumably caused by disuse of the affected limb.

Bone-loading physical activity may decrease or prevent the postfracture deterioration of bone properties. As summarized in meta-analyses and reviews,[9–11] the most effective physical activity programs for increasing or preserving bone health in older populations incorporate progressive resistance and power training, weight-bearing impact loading activities, or challenging balance and agility training. Most of the previous studies have, however, focused on relatively healthy populations, whereas only a few studies have been performed in the frail elderly,[12–14] and even fewer in hip fracture patients.[15,16] Furthermore, the findings from the limited number of trials examining the effects of exercise on bone structure, strength, and volumetric density (vBMD) in older people are conflicting[17–22] and no studies involving 3D bone characterization have been conducted in hip fracture patients or subjects comparable to them. Thus, it is currently unclear whether fragile bones, such as those in older hip fracture patients, are able to adapt to increased loading.

To date, no attempts have been made to investigate the effects of physical exercise on bone structural and densitometric traits of both legs after hip fracture. Although exercise has increased muscle strength and functional capacity in older people with a recent hip fracture,[15,23,24] the osteogenic effects remain unclear. We hypothesized that a 12-month home-based physical rehabilitation program, including weight-bearing exercises, would be feasible and effective in reducing postfractural losses in tibial bone density, structure, and strength in older people recovering from a recent hip fracture.

Subjects and Methods

Design and participants

This study was a 12-month randomized controlled trial (RCT; ISRCTN53680197; Fig. 1) investigating the effects of a home-based rehabilitation program on mobility recovery among community-dwelling older people with a recent hip fracture.[25] This secondary analysis reports the effects of the intervention on tibial bone traits. The design and recruitment procedure have been published in detail before.[26] Briefly, patient records at the Central Finland Central Hospital (Jyväskylä, Finland) were reviewed to recruit all ambulatory and community-dwelling men and women over age 60 years who had been operated for a femoral neck or pretrochanteric fracture (ICD code S72.0 or S72.1) between 1.3.2008 and 31.12.2010, and were resident in the catchment area. In total, 269 men and women were informed about the study. Of these, 161 expressed interest in the study and were visited by a researcher during their inpatient stay at the health care center for a preliminary assessment of eligibility. Thereafter, 136 persons were invited to the baseline measurements, of whom 81 eligible patients participated in the study. The exclusion criteria were severe memory problems (Mini Mental State Examination <18), alcoholism, a severe cardiovascular or pulmonary condition or some other progressive disease, and severe depression (Beck Depression Inventory >29).

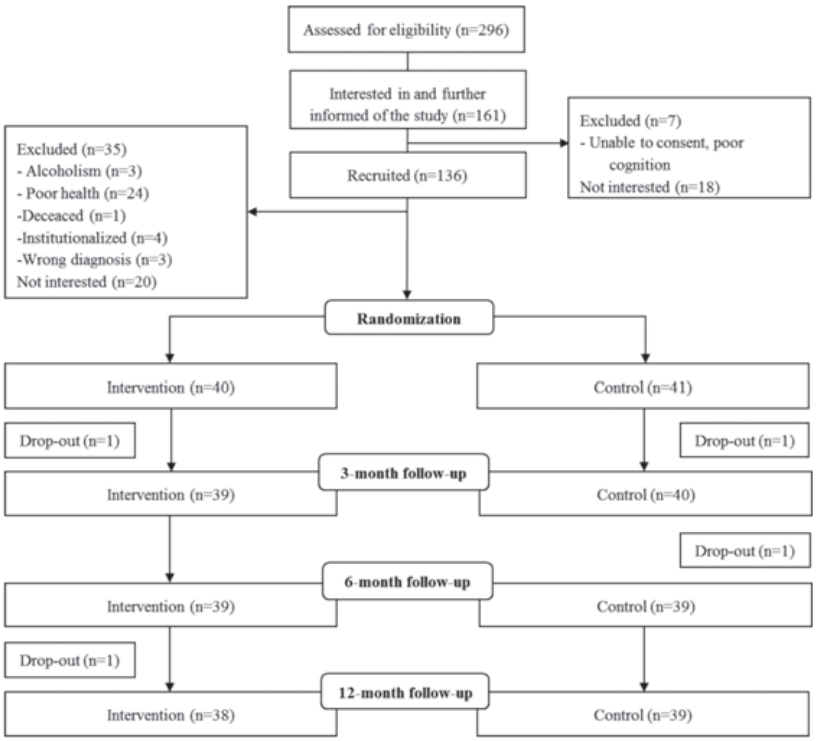

Fig. 1. Flowchart of the study.

After the baseline measurements, conducted on average 10 weeks postfracture, the participants were randomized into an intervention ($n = 40$) and a standard care control ($n = 41$) group using a computer-generated group allocation list generated by a blinded statistician, who was not involved in either the recruitment or data collection processes. Blocks of 10, stratified by gender and surgical procedure (internal fixation versus arthroplasty), were used.

Follow-up measurements were arranged at 3, 6, and 12 months after the baseline measurements. All assessments were conducted at the research laboratory. All outcome assessors were blinded to the treatment-group assignment. All participants gave their written informed consent and permission to review their medical records prior to participation in the study. The study was approved by the Ethics Committee of the Central Finland Health Care District (Dnro56/2007) and conformed to the principles of the Declaration of Helsinki.

Peripheral quantitative computed tomography

Properties of the distal tibia and tibial shaft of both legs were assessed by pQCT (XCT-2000; Stratec Medizintechnik, Pforzheim, Germany). The pQCT device was calibrated daily using a standard phantom and monthly using a cone phantom provided by the manufacturer. The distal tibia was defined as 5% and tibial shaft as 55% of the measured tibial length proximal to the distal end plate. The scan line was adjusted using the scout view of the pQCT system. Tibial length was defined as the distance between the lateral malleolus and the lateral condyle of the tibia. A single (2.4-mm) axial slice with a voxel size of 0.8 × 0.8 mm, typical tube voltage of 46 kV, tube current of 0.3 mA, and scan speed of 20 mm/s was obtained.

The images were analyzed with an automated threshold-free cortical bone detection method (the outer boundary detection and subsequent shrinking [OBS] procedure, OBS cortical bone detection 2.1).[27,28] For the distal tibia, compressive bone strength index (BSI, $g^2/cm^4 = vBMD_{TOT}{}^2 \times CSA_{TOT}$),[29,30] total volumetric BMD ($vBMD_{TOT}$, mg/cm^3), and total cross-sectional area (CSA_{TOT}, mm^2) were determined. The parameters for the tibia midshaft site were the strength-strain index (SSI, mm^3; density-weighted polar section modulus), reflecting the bone's resistance to bending and torsional loads, cortical vBMD ($vBMD_{CO}$), and the ratio of cortical to total area (CSA_{CO}/CSA_{TOT}). The root mean square coefficient of variation (CV_{RMS}) for the BMD, structure, and strength index measurements in our laboratory ranges from 0.4% to 1.6%.[31]

Health, fracture status, and anthropometry

At baseline, during a medical examination performed by a research nurse and a physician, the presence of chronic conditions, use of prescription medications, fracture date and status, and type and date of surgery were confirmed with a prestructured questionnaire, current prescriptions, and medical records. Contraindications for the physical performance assessments and the intervention were evaluated according to the American College of Sports Medicine guidelines.[32] Blood count, C-reactive protein, and hemoglobin analyses were performed to evaluate possible acute conditions before the performance measurements. Body height and weight were measured using a stadiometer and a digital scale, and BMI was calculated as body weight divided by height squared (kg/m^2). Body fat percentage was assessed with a bioimpedance devise with eight polar electrodes (BC-418; TANITA, Tokyo, Japan). Blood samples were drawn from the antecubital vein in the morning. Specimens were centrifuged and frozen at −80°C until analysis. Serum concentrations of 25-hydroxyvitamin D (25OHD; nmol/L) and parathyroid hormone (PTH, ng/L) were determined at baseline using an electrochemiluminescence immunoassay and a chemiluminescence immunoassay (Modular Analytics E170; Roche Diagnostics, Mannheim, Germany), respectively. The intra-assay CV for 25OHD was 1.1% to 2.0% (26.7 to 261 ng/L), and for PTH it was 2.2% to 6.8% (16.9 to 168 nmol/L). Smoking history and alcohol consumption were assessed by questionnaire.

Physical activity and physical performance

Current level of physical activity (PA) was assessed by a slightly modified Grimby scale[33] with seven response alternatives: (1) mainly resting, (2) most activities performed in a sitting position, (3) light PA twice a week at most, (4) moderate PA or housework about 3 hours a week, (5) moderate PA or housework at least 4 hours a week or heavy PA $\leq$ 4 hours a week, (6) physical exercise or heavy leisure time PA several times a week, and (7) competitive sports several times a week. The responses were recoded for analyses as inactivity (categories 1 to 2), light PA (category 3), and moderate-to-heavy PA (categories 4 to 7).[34] Physical performance was assessed according to the Short Physical Performance Battery, which includes habitual walking speed, chair rise, and balance tests.[35] A higher score (range, 0 to 12) indicates better performance. Maximal isometric knee extension force of the fractured and nonfractured leg was measured in a sitting position using an adjustable dynamometer chair (Good Strength; Metitur Ltd, Palokka, Finland).[36] The ankle was attached to a strain-gauge system with the knee angle fixed at 120 degrees. After two to three submaximal practice trials, three maximal trials were recorded and further trials performed until no further improvement occurred. Each maximal effort was maintained for 2 to 3 s, separated by a 30-s rest. The highest recorded force value was used for the analysis. Leg extension power of each leg was measured with the Nottingham Leg Extensor Power Rig in an upright sitting position.[37,38] The distance between the seat and the push-pedal was adjusted for leg length. The measurement was repeated until no further improvement occurred; the best performance was used in the analyses. In our laboratory, the test–retest CVs for the force and power measurements were 6%[36] and 8%,[38] respectively.

Intervention

The intervention group received a year-long, physical rehabilitation program aimed at restoring mobility and physical functional capacity to the pre hip fracture level.[25,26] The individually tailored program comprised an evaluation and modification of environmental hazards,[39] guidance for safe walking, nonpharmacological pain management, motivational physical activity counseling, and a progressive home exercise program. The intervention took place in the participants' homes and included five to six home visits by a physiotherapist.

The progressive home exercise program comprised strengthening and stretching exercises for the lower limb muscles, balance training in the standing position, and functional exercises including walking, reaching, turning in different directions, and stair climbing. All exercises were weight-bearing. The program was progressively increased in intensity and demandingness 4 to 5 times. The strengthening and stretching exercises (performed on the same day, 3 times per week), and

the balance and functional exercises (performed on the same day, 2 to 3 times per week) were performed on nonconsecutive days. Each training session lasted approximately 30 minutes. The strengthening exercises included knee extension and flexion, hip abduction, plantar flexion, chair rising, and squatting. In the strengthening exercises, the resistance was progressively increased with resistance bands of three different strengths. Functional exercises were performed only during the first 12 weeks. All participants in the intervention group kept a daily exercise diary. Motivational physical activity counseling was delivered as two face-to-face sessions (at 3 and 6 months) and three phone contacts (at 4, 8, and 10 months).

Control condition

Information on standard care after hip fracture was collected by interview at baseline. In total, 68% of the intervention group and 71% of the controls ($p = 0.813$) reported having received a home exercise program from the hospital or the health care center. Typically, the program comprised five to seven exercises for the lower limbs (mostly the fractured leg) without additional resistance or progression.[26] Compliance with the home exercise program was not monitored and the program was not increased in intensity. Five intervention participants and seven controls were referred for physiotherapy.

Statistical analysis

The study power, calculated for the main outcome, mobility limitation, was 78%. Mean values, standard deviations and standard errors were calculated using standard procedures. All outcome variables were analyzed according to the intention-to-treat principles. Baseline characteristics were compared by cross-tabulation and chi-square tests for discrete variables, by independent samples *t* test for normally distributed data, and by the Mann-Whitney *U* test for non-normally distributed continuous data. The normality of the distributions was tested with the Shapiro-Wilk test. The effect of the intervention was assessed using an interaction term (group × time) in a general linear model for longitudinal data estimated in Mplus, version 7.4.[40] The models were adjusted by age, keeping the age effect constant over time. An additional analysis was performed by adjusting the models by age, sex, and body weight, but the results were not different from the main analysis (data not shown). We assumed that missing data were missing-not-at-random (MNAR); hence, for example, we used the maximum likelihood-based pattern-matching model[41] to include the data from dropouts in the statistical data analysis up to the time of loss to follow-up. The main reasons for missing bone data were inability to perform the measurements, inaccurate positioning of the leg, a technically invalid pQCT scan, substantial movement artifacts, and metal in tissues in the scanned region. For the distal tibia, 154 valid scans were obtained at baseline, 133 at 3 months, 137 at 6 months, and 130 at 12 months. For the midshaft site, the corresponding numbers were 156, 136, 134, and 130. A per protocol analysis on the effect of the intervention was also performed. For this analysis, only subjects whose overall compliance with physical exercises was over 70% ($n = 16$) were chosen from the intervention group. In addition, sensitivity analyses were performed by restricting the analyses to women (intervention group, $n = 31$; control group, $n = 32$). Descriptive analyses were performed using SPSS 24.0 software (IBM, Armonk, NY, USA) and the general linear model extended for MNAR longitudinal data was analyzed using Mplus 7.4 with the significance level set to 5%. Mean changes were calculated as (follow-up − baseline), and mean percentage changes were calculated as [(follow-up − baseline)/baseline × 100]. Side-to-side differences in bone variables were defined as (nonfractured leg − fractured leg). Compliance with the intervention was calculated using the following formula: (number of performed exercises)/(expected number of exercises) × 100.

Results

No differences were observed between the intervention and control groups in baseline characteristics (Table 1). Mean serum concentrations of 25OHD and PTH were normal. In total, 28 participants had a serum 25OHD level below 50 nmol/L. Seven of these 28 had values below 25 nmol/l. Based on medical records and questionnaires collected at baseline and at 3, 6, and 12 months, 13 intervention participants and 14 controls reported taking bisphosphonates during the 12-month intervention. In addition, one participant in the intervention group reported receiving strontium ranelate. In the per protocol analysis, no significant between-group differences were observed in baseline characteristics.

Intervention adherence and adverse events

During the 12-month study, one intervention participant and two controls dropped out for personal reasons, and one intervention participant died from cardiac failure unrelated to the intervention before the 12-month measurements. No intervention-related adverse events occurred. Four intervention participants were suspended by a physician for medical reasons during the first 6 months of the study. Two of them returned to the intervention (revision operation, femoral fracture), but 2 were unable to continue (pneumonia and new hip fracture, pulmonary embolism). During the final 6 months, 5 participants were suspended (pubic bone fracture, urinary tract infection, cerebral infarction, cardiac failure, sacrum strain fracture) and none of them returned. In the control group, four revision operations were performed.

Compliance with physical exercises

Overall compliance with the exercises was 50% for the strengthening, 45% for the stretching, 54% for the balance, and 69% for the functional exercises. During the first 6 months, compliance was 61% for the strengthening, 53% for the stretching, and 65% for the balance exercises. During the last 6 months, the corresponding values were 39%, 37%, and 43%. Compliance with the first face-to-face physical activity counseling session was 97%, and with the following sessions as follows: 90% (first phone contact), 87% (second face-to-face), and 85% (second phone contact), and 79% (third phone contact).

Muscle force and power

The intervention had no effect (group × time) on maximal isometric knee extension force or leg extension power. Fractured side force and power increased significantly in both groups (time effect, 12 months, $p < 0.001$): 24% and 32%, respectively, in the intervention group and 26% and 35% in the control group. Leg extension power of the nonfractured leg increased significantly in both groups (time effect, 12 months, $p = 0.001$): 4% in the intervention group and 15% in the control group.

Table 1. Baseline characteristics of the participants.

	Intervention ($n = 40$)	Control ($n = 41$)
Age, years	80.9 (7.7)	79.1 (6.4)
Women, *n* (%)	31 (78)	32 (78)
Height, cm	160.9 (8.9)	160.3 (9.1)[a]
Weight, kg	65.8 (11.9)	65.9 (11.3)
BMI, kg/m^2	25.3 (3.6)	25.6 (3.9)[a]
Body fat, %	30.5 (7.1)[b]	32.2 (5.8)[b]
Hemoglobin, g/L	127 (13)	130 (13)
Lowest hemoglobin after surgery, g/L	98 (11)	99 (15)
Smoking, *n* (%)		
Never	34 (85)	30 (73)
Former	4 (10)	6 (15)
Current	2 (5)	5 (12)
Number of chronic diseases	3 (2)	3 (2)
Current bisphosphonate use, *n* (%)	9 (23)	7 (17)
Oral corticosteroid use, *n* (%)	1 (2.5)	1 (2.4)
Serum-25OHD, nmol/L	57 (22)[c]	54 (24)[d]
Serum-PTH, ng/L	49 (23)[c]	49 (23)[d]
Site of fracture, *n* (%)		
Femoral neck	27 (68)	25 (61)
Pertrochanteric	13 (33)	16 (39)
Type of surgery, *n* (%)		
Internal fixation	19 (48)	19 (46)
Hemiarthroplasty	15 (38)	18 (44)
Total arthroplasty	6 (15)	4 (10)
Time since fracture (days)	68 (16)	71 (37)
Level of physical activity, *n* (%)		
Inactivity (mostly sitting)	15 (38)	11 (28)
Light activity	23 (58)	25 (63)
Moderate-to-heavy activity	2 (5)	4 (10)
Physical performance		
SPPB score	5.8 (2.5)	6.6 (2.2)
Knee extension force, *N*		
Fractured side	185.1 (73.1)[e]	168.3 (71.6)[a]
Nonfractured side	240.4 (93.4)[b]	228.3 (83.9)[a]
Leg extension power, W		
Fractured side	55.9 (29.5)[c]	51.1 (28.6)[b]
Nonfractured side	73.9 (37.1)[d]	73.8 (40.6)[f]

Values are means (SD) or n (%) unless otherwise noted.
[a]$n = 40$.
[b]$n = 38$.
[c]$n = 32$.
[d]$n = 36$.
[e]$n = 34$.
[f]$n = 39$.
SPPB = short physical performance battery.

Bone properties

The intervention had no effect (group × time) on the distal tibia or midtibial bone traits (Tables 2 and 3). At the distal site (Table 2 and Fig. 2) at 3 months, $vBMD_{TOT}$ of both legs and BSI of the fractured leg had decreased significantly in both groups, whereas at 6 months, $vBMD_{TOT}$ of the fractured leg and BSI of both legs had decreased in both groups. At 12 months, $vBMD_{TOT}$ of the fractured leg, CSA_{TOT} of the nonfractured leg and BSI of both legs had decreased significantly in both groups. The mean decrease in $vBMD_{TOT}$ from baseline to 12 months on the fractured side was 1.9% in the intervention group and 1.5% in the control group. The values for CSA_{TOT} on the nonfractured side were 0.7% and 1.0%. In the intervention group, the mean decrease in BSI was 3.1% in the fractured leg and 2.3% in the nonfractured leg, whereas in the control group the corresponding values were 2.7% and 2.0%. A significant group difference over follow-up time was observed in side-to-side difference in CSA_{TOT} favoring the nonfractured leg in the intervention group and fractured leg in the control group, respectively.

At the midshaft site (Table 3 and Fig. 3), $vBMD_{CO}$ of the fractured side leg decreased significantly over time in both groups at 3, 6, and 12 months, whereas CSA_{CO}/CSA_{TOT} and SSI of both legs decreased significantly over 12 months in both groups. The mean decrease in $vBMD_{CO}$ from baseline to 12 months on the fractured side was 1.1% in the intervention

group and 1.5% in the control group. On the fractured side, the corresponding values for CSA_{CO}/CSA_{TOT} were 1.9% and 1.1%, and on the nonfractured side 1.1% and 1.3%, for the intervention group and controls, respectively. SSI on the fractured side decreased by 1.7% in the intervention group and 1.9% in the control group, whereas on the nonfractured side the decrease was 1.4% and 1.3%. Side-to-side difference in $vBMD_{CO}$ increased significantly over 12 months in both groups favoring the nonfractured leg.

The changes in the bone outcomes were not systematically associated with the changes in maximal isometric knee extension force and leg extension power (data not shown).

No significant interaction effects were observed in the analyses restricted to women only, except for CSA_{TOT} of the nonfractured leg and CSA_{CO}/CSA_{TOT} of the fractured leg. In the intervention group compared with controls, CSA_{TOT} of the nonfractured leg decreased significantly at 3 months ($p = 0.047$), whereas at 6 months CSA_{CO}/CSA_{TOT} of the fractured leg decreased significantly more in the intervention group compared with controls ($p = 0.019$).

Per protocol analysis

No intervention effect was observed in the distal tibia or midtibial bone traits (Supplemental Tables S1 and S2).

Discussion

This 12-month home-based physical rehabilitation program on mobility recovery had no effect on the distal tibia or tibial midshaft bone traits of community-dwelling men and women over age 60 years recovering from a hip fracture. The bone structural and densitometric traits of both legs continued to deteriorate during the year following the fracture. At both bone sites, bone loss was more evident in the fractured leg, especially in total and cortical density.

The present findings are in line with those previously reported for the effects of physical rehabilitation on bone traits after hip fracture. To our knowledge, only two intervention studies have been conducted.[15,16] Orwig and colleagues[16] conducted an RCT of a 12-month low-intensity home exercise program for older women with a recent hip fracture. Compared with controls receiving usual care, the intervention did not result in significant changes in contralateral hip aBMD. Similarly, a more-intensive 6-month outpatient rehabilitation program including progressive resistance training did not improve hip or total body aBMD compared with a low-intensity home-exercise program.[15] Studies with osteoporotic participants comparable to hip fracture patients have also revealed minor or no effects on bone density.[12,42] A nine-month program including progressive strength and endurance training did not increase aBMD in fragile, elderly men and women.[13] Similarly, a long-term (2.5 years) impact training program had no effect on aBMD in older women with weak bones, although the BMC of the femoral neck decreased significantly less in the intervention group compared with controls.[14]

The absence of training-induced improvements in previous studies as well as in the present study could be related to the low muscular capacity of the elderly subjects, which may have limited their ability to produce the peak forces required for bone adaptation. In addition, the programs may have lacked intensity and specificity for bone adaptation. In contrast, our previous study on middle-aged and older male athletes with

Table 2. Distal tibia bone traits at baseline and at different follow-up points, and *p*-values for group, time and interaction effects. Intention-totreat analysis.

			$vBMD_{TOT}$ (mg/cm^3)			CSA_{TOT} (mm^2)			BSI (g^2/cm^4)		
Group	Time		Fractured leg	Nonfractured leg	Side-to-side difference	Fractured leg	Nonfractured leg	Side-to-side difference	Fractured leg	Nonfractured leg	Side-to-side difference
Intervention	Baseline		225 (8)	227 (8)	0.6 (2.4)	1020 (26)	1046 (26)	25 (8)	0.54 (0.04)	0.56 (0.04)	0.011 (0.010)
	3 months		222 (8)	226 (8)	2.5 (2.4)	1017 (26)	1037 (27)	16 (8)	0.53 (0.04)	0.55 (0.04)	0.017 (0.010)
	6 months		221 (8)	224 (8)	1.8 (2.3)	1022 (25)	1036 (25)	10 (7)	0.53 (0.04)	0.54 (0.04)	0.010 (0.010)
	12 months		221 (8)	224 (8)	3.0 (2.3)	1023 (25)	1039 (25)	9 (9)	0.53 (0.04)	0.54 (0.04)	0.017 (0.010)
Control	Baseline		207 (8)	209 (8)	5.1 (2.3)	1032 (26)	1033 (25)	−5 (8)	0.46 (0.04)	0.47 (0.04)	0.019 (0.010)
	3 months		205 (8)	207 (8)	5.7 (2.3)	1032 (26)	1035 (26)	−2 (8)	0.45 (0.04)	0.47 (0.04)	0.025 (0.010)
	6 months		204 (8)	208 (8)	5.7 (2.3)	1031 (25)	1030 (24)	−4 (7)	0.45 (0.04)	0.47 (0.04)	0.022 (0.010)
	12 months		204 (8)	207 (8)	6.6 (2.2)	1036 (25)	1022 (24)	−18 (8)	0.45 (0.04)	0.46 (0.04)	0.020 (0.009)
p-value	Group		0.109	0.119	0.178	0.733	0.718	0.006	0.131	0.123	0.570
	Time	3	0.007	0.023	0.527	0.914	0.718	0.623	0.005	0.183	0.127
		6	0.033	0.083	0.573	0.797	0.735	0.910	0.009	0.043	0.502
		12	0.012	0.176	0.127	0.541	0.043	0.079	0.016	0.018	0.949
	Group × time	3	0.714	0.432	0.320	0.785	0.132	0.184	0.579	0.312	0.974
		6	0.424	0.347	0.688	0.604	0.404	0.096	0.700	0.076	0.518
		12	0.553	0.540	0.544	0.999	0.659	0.813	0.568	0.567	0.348

Values are estimated mean (SE). Side-to-side differences calculated as (nonfractured leg – fractured leg).
$vBMD_{TOT}$ = total volumetric BMD; CSA_{TOT} = total cross-sectional area; BSI = compressive bone strength index.

Table 3. Tibial mid-shaft bone traits at baseline and at different follow-up points, and p-values for group, time and interaction effects. Intentionto- treat analysis.

Group	Time	$vBMD_{CO}$ (mg/cm^3)			CSA_{CO}/CSA_{TOT}			SSI (mm^3)		
		Fractured leg	Nonfractured leg	Side-to-side difference	Fractured leg	Nonfractured leg	Side-to-side difference	Fractured leg	Nonfractured leg	Side-to-side difference
Intervention	Baseline	1050 (10)	1057 (12)	5.7 (6)	0.576 (0.015)	0.581 (0.016)	0.007 (0.008)	1524 (70)	1571 (72)	43 (27)
	3 months	1047 (11)	1053 (12)	4.7 (6)	0.574 (0.016)	0.582 (0.015)	0.010 (0.008)	1513 (73)	1562 (74)	50 (26)
	6 months	1043 (11)	1051 (12)	5.5 (7)	0.570 (0.016)	0.578 (0.016)	0.011 (0.008)	1501 (72)	1558 (74)	58 (26)
	12 months	1039 (12)	1049 (12)	7.5 (7)	0.565 (0.016)	0.575 (0.016)	0.012 (0.008)	1497 (73)	1549 (73)	48 (26)
Control	Baseline	1035 (11)	1032 (11)	−1.7 (6)	0.552 (0.015)	0.551 (0.015)	0.005 (0.007)	1456 (71)	1460 (69)	11 (26)
	3 months	1029 (11)	1030 (12)	1.1 (6)	0.550 (0.016)	0.551 (0.015)	0.007 (0.008)	1458 (73)	1463 (72)	15 (25)
	6 months	1026 (11)	1030 (12)	3.6 (6)	0.552 (0.016)	0.547 (0.015)	0.003 (0.007)	1446 (72)	1456 (72)	16 (25)
	12 months	1020 (12)	1027 (12)	9.0 (7)	0.546 (0.016)	0.544 (0.015)	0.003 (0.008)	1429 (73)	1441 (70)	21 (25)
p-value	Group	0.306	0.129	0.403	0.278	0.165	0.829	0.500	0.268	0.397
	Time 3	0.028	0.444	0.502	0.153	0.883	0.317	0.800	0.679	0.749
	6	0.004	0.475	0.108	0.688	0.085	0.386	0.324	0.656	0.644
	12	<0.001	0.099	0.004	0.025	0.001	0.547	0.012	0.021	0.273
	Group × time 3	0.531	0.671	0.530	0.622	0.624	0.969	0.324	0.318	0.864
	6	0.829	0.328	0.257	0.069	0.778	0.105	0.153	0.496	0.516
	12	0.482	0.475	0.108	0.215	0.833	0.144	0.969	0.864	0.685

Values are estimated mean (SE). Side-to-side differences calculated as (non-fractured leg – fractured leg).
$vBMD_{CO}$ = cortical volumetric BMD, CSA_{CO}/CSA_{TOT} = ratio of cortical to total area, SSI = strength-strain index.

above-average muscle characteristics[21] showed significant improvements in tibial structure and strength after novel, intensive strength and sprint training, suggesting that in the presence of high-intensity loading and with sufficient muscle strength the adaptability of aging bone structure is maintained. This potential explanation is also supported by animal and human studies demonstrating that given the right stimulus, bone mechanoresponsiveness remains largely unaltered with aging,[43,44] although some decrease in mechanosensitivity may occur.[45] In the present study, the primary target was not bone traits per se, the intensity of the rehabilitation program was relatively low, and no effects on bone structure and strength were observed. Although all the exercises were weight-bearing and elastic resistance bands of different strengths were used, it is plausible that the program did not provide a sufficient stimulus for osteogenic adaptations. Although muscle force and power increased significantly over time in both groups (no between-group differences), the levels might nevertheless have been too low and the strains generated not novel enough to stimulate bone formation. Moreover, compliance with the strengthening as well as other physical exercises may not have been sufficient for bone adaptation, especially during the last 6 months of the intervention.

In this study, as in our previous cross-sectional study on hip fracture patients,[2] bone deterioration was more evident in the fractured than nonfractured leg, both at the distal tibia and midshaft sites. At the midshaft site, a side-to-side difference in cortical density increased significantly over time in both groups favoring the nonfractured leg. In our previous cross-sectional study,[2] lower bone characteristics were manifested as decreased BMC and geometrical properties, and no side-to-side or between-group differences were observed in vBMD. In the present study, by contrast, vBMD on the fractured side decreased significantly at both bone sites. At the midshaft site, bone deterioration in the nonfractured leg was manifested as a decrease in the SSI and the ratio of cortical to total area, whereas on the fractured side, bone loss was also evident in volumetric cortical density. Based on the results of high-resolution CT exploration of age-related bone loss, which have shown intracortical bone loss and resulting increased cortical porosity,[46] we assumed that in our sample intracortical bone loss was more pronounced in the fractured leg than nonfractured leg.

Several issues merit further discussion. Our study sample was rather heterogeneous in participant age, physical functional capacity, and bone properties, factors that help to explain the large individual variability in the bone results. The inclusion of both sexes also increased variability and may have affected the results. Owing to their larger skeletal size and higher bone mass, men generally have more robust bone characteristics. In addition, the changes in bone density and structure after hip fracture may in part be different between the sexes.[4,5] The differences in posthip fracture BMD changes could also be related to the accelerated bone loss in older men compared with the attenuated decline in women for whom bone loss follows menopause and thus occurs earlier.[4] Furthermore, one-third of our participants were using bisphosphonates (no difference between the groups), which again may have affected the results. Bisphosphonates increase BMD by inhibiting bone resorption by osteoclasts, which may suppress bone remodeling and, after long-term usage, possibly limit the bone cell response to exercise. In the present study, the results restricted to women did not differ from the main analysis. The sample size, especially in the restricted analyses was, however, rather small. The

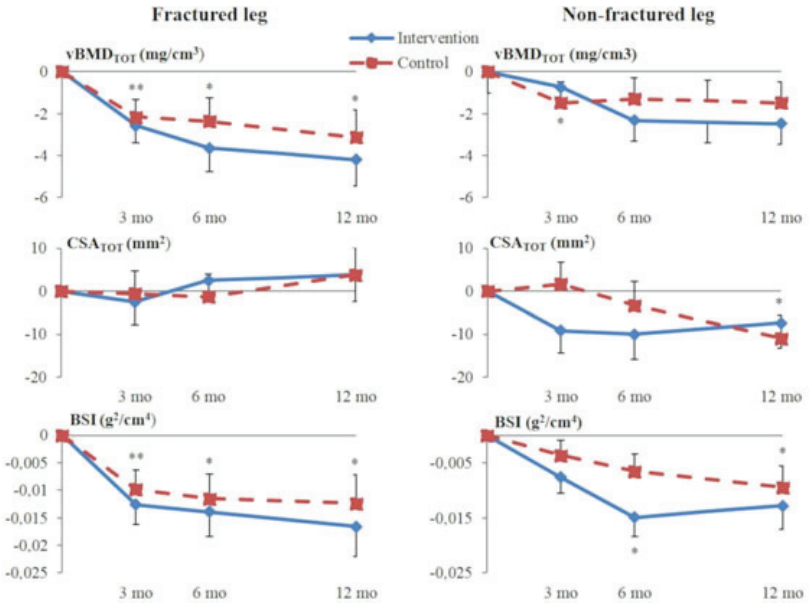

Fig. 2. Mean change relative to baseline values for $vBMD_{TOT}$, CSA_{TOT}, and compressive bone strength index of the distal tibia. (Mean, SE) $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ for the time effect at different time points. Intention-to-treat analysis. $vBMD_{TOT}$ = total volumetric BMD; CSA_{TOT} = total cross-sectional area; BSI = compressive bone strength index.

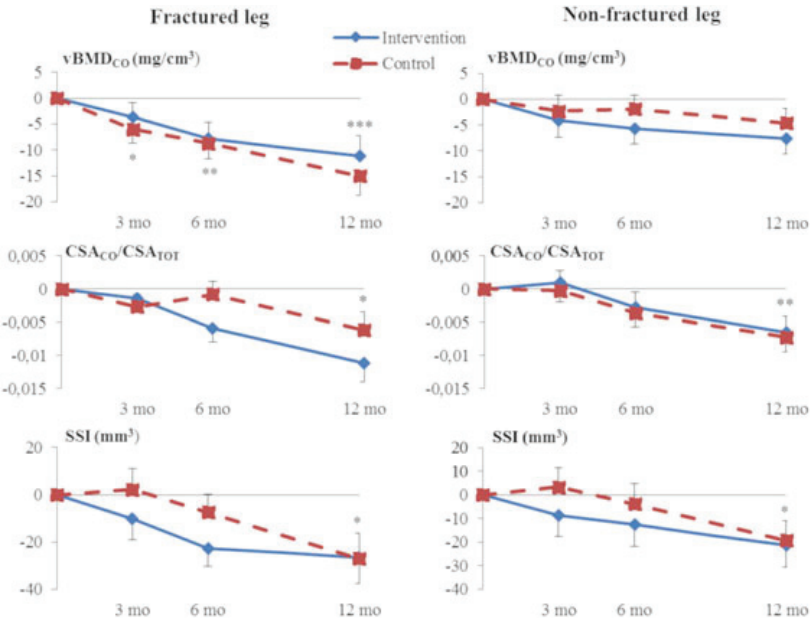

Fig. 3. Mean change relative to baseline values for $vBMD_{CO}$, CSA_{CO}/CSA_{TOT}, and strength-strain index of the tibial midshaft. (Mean, SE) $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ for the time effect at different time points. Intention-to-treat analysis. $vBMD_{TOT}$ = total volumetric BMD; CSA_{CO}/CSA_{TOT} = ratio of cortical to total area; SSI = strength–strain index.

number of participants was insufficient for subsample analysis of the effect of bisphosphonates on the results.

This study has its limitations. Most importantly, the study reports secondary outcomes of an RCT. The home exercise program was not specifically designed to improve bone strength, and probably lacked the intensity and specificity needed for bone adaptation. Furthermore, owing to the inclusion criteria, our participants were probably healthier than hip fracture patients on average, a factor that should be considered when generalizing the results. However, for the frailest patients, a program of this kind would not be advisable. Inclusion of measures of the proximal femur would have added value to our study. Because of the imaging modality used, our results are not fully comparable with those of previous studies. A few methodological considerations also be kept in mind when interpreting the results. pQCT, the imaging method used in this study, is susceptible to partial volume effect and beam hardening. In addition, a higher scan resolution would have provided more detailed results. Finally, the amount of missing data was considerable, partly because of the frailty of the study population. We were, however, able to account for this by using a specifically tailored maximum likelihood estimation method.

The strengths of this study include a randomized controlled study design and the use of a 3D imaging modality to examine changes in bone geometry and volumetric density. Our study was the first trial to examine the effect of physical exercise on bone properties of both the fractured and nonfractured leg in hip fracture patients. Furthermore, we used a theory-based approach to the assessments and the intervention, and investigated a topic that has high clinical and societal relevance. Moreover, the home-based physical rehabilitation program eliminated the burden of traveling to a facility, it was individually tailored, and it included visits by a physiotherapist as well as motivational physical activity counseling. Despite no effect on bone, the rehabilitation program increased physical activity[34] and improved mobility recovery.[25] The intervention was well-tolerated, the program was feasible in the home setting, and the dropout rate was low. Compliance with the home exercises was moderate and comparable to that reported in other similar studies.[47,48] Compliance with the physical activity counseling was excellent. Finally, the one-year follow-up was of sufficient duration to detect changes in bone, and bone data were gathered at multiple time points.

In conclusion, our home-based physical rehabilitation was unable to prevent bone deterioration in older people after hip fracture. Tibial bone traits, both cortical and trabecular, continued to weaken during the year following the fracture, on both the fractured and nonfractured side. Together with decreased muscle strength, deterioration in bone properties markedly increases the risk for a second fracture; hence, specific interventions targeting bones and muscles should be developed to maximize postfracture recovery and minimize deterioration. Improving muscle function and balance to reduce the risk of recurrent falls and fractures may be a more feasible intervention target after hip fracture, especially because preventing bone deterioration seems unlikely. More research is, however, needed to find out whether fragile bones, such as those in older hip fracture patients, are able to adapt to increased physical loading, and what type of exercise would be safe, feasible, and effective.

Disclosures

All authors state that they have no conflicts of interest.

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Supplemental Table 1. Distal tibia bone traits at baseline and at different follow-up points, and p-values for group, time and interaction effects. Per protocol analysis.

			$vBMD_{TOT}$ (mg/cm^3)			CSA_{TOT} (mm^2)			BSI (g^2/cm^4)		
Group	Time		Fractured leg	Non-fractured leg	Side-to-side difference	Fractured leg	Non-fractured leg	Side-to-side difference	Fractured leg	Non-fractured leg	Side-to-side difference
Intervention	Baseline		218 (12)	220 (13)	1.6 (4.1)	1030 (42)	1043 (44)	26 (13)	0.52 (0.06)	0.53 (0.04)	0.016 (0.017)
	3 months		218 (12)	219 (13)	1.9 (4.0)	1028 (43)	1042 (46)	23 (14)	0.52 (0.06)	0.52 (0.04)	0.016 (0.017)
	6 months		217 (12)	219 (13)	2.0 (3.9)	1032 (41)	1027 (42)	6 (12)	0.51 (0.04)	0.51 (0.04)	0.007 (0.017)
	12 months		218 (12)	220 (13)	3.3 (3.9)	1034 (39)	1036 (42)	10 (14)	0.52 (0.04)	0.53 (0.04)	0.018 (0.016)
Control	Baseline		207 (8)	210 (8)	5.1 (2.5)	1029 (27)	1031 (26)	-5 (8)	0.46 (0.04)	0.48 (0.06)	0.020 (0.010)
	3 months		205 (8)	208 (8)	5.7 (2.4)	1028 (27)	1033 (27)	-2 (9)	0.45 (0.04)	0.47 (0.06)	0.025 (0.010)
	6 months		205 (8)	208 (8)	5.7 (2.4)	1028 (26)	1027 (26)	-4 (8)	0.45 (0.04)	0.47 (0.06)	0.023 (0.010)
	12 months		204 (8)	208 (8)	6.6 (2.4)	1033 (25)	1019 (25)	-19 (9)	0.45 (0.04)	0.47 (0.06)	0.019 (0.010)
p-value	Group		0.436	0.499	0.462	0.928	0.803	0.048	0.453	0.474	0.858
	Time	3	0.005	0.020	0.511	0.902	0.657	0.609	0.002	0.124	0.124
		6	0.023	0.074	0.526	0.783	0.540	0.888	0.005	0.026	0.465
		12	0.010	0.140	0.095	0.527	0.030	0.058	0.010	0.006	0.940
	Group	3	0.469	0.444	0.859	0.923	0.701	0.623	0.128	0.973	0.411
	× time	6	0.227	0.890	0.902	0.987	0.247	0.081	0.216	0.253	0.157
		12	0.606	0.425	0.907	0.451	0.678	0.894	0.145	0.214	0.752

Values are estimated mean (SE). $vBMD_{TOT}$ = total volumetric BMD, CSA_{TOT} = total cross-sectional area, BSI = compressive bone strength index. Side-to-side differences calculated as (non-fractured leg – fractured leg).

Supplemental Table 2. Tibial mid-shaft bone traits at baseline and at different follow-up points, and p-values for group, time and interaction effects. Per protocol analysis.

Group	Time		$vBMD_{CO}$ (mg/cm^3)			CSA_{CO}/CSA_{TOT}			SSI (mm^3)		
			Fractured leg	Non-fractured leg	Side-to-side difference	Fractured leg	Non-fractured leg	Side-to-side difference	Fractured leg	Non-fractured leg	Side-to-side difference
Intervention	Baseline		1048 (18)	1048 (21)	-0.8 (10.6)	0.577 (0.026)	0.588 (0.027)	0.014 (0.013)	1493 (117)	1555 (117)	50 (45)
	3 months		1047 (18)	1042 (21)	-3.4 (10.6)	0.574 (0.026)	0.588 (0.026)	0.018 (0.012)	1491 (122)	1544 (121)	52 (40)
	6 months		1044 (19)	1040 (21)	-2.5 (10.8)	0.573 (0.026)	0.583 (0.027)	0.015 (0.012)	1481 (120)	1550 (122)	61 (43)
	12 months		1042 (20)	1045 (21)	1.4 (11.1)	0.570 (0.026)	0.581 (0.026)	0.014 (0.013)	1479 (121)	1533 (118)	44 (43)
Control	Baseline		1038 (11)	1036 (12)	-1.6 (6.5)	0.556 (0.016)	0.556 (0.016)	0.005 (0.008)	1457 (74)	1461 (71)	11 (28)
	3 months		1032 (12)	1033 (13)	0.9 (6.6)	0.553 (0.017)	0.556 (0.016)	0.007 (0.008)	1459 (77)	1464 (73)	15 (25)
	6 months		1029 (12)	1033 (13)	3.6 (6.6)	0.555 (0.017)	0.553 (0.016)	0.003 (0.008)	1451 (76)	1457 (74)	15 (26)
	12 months		1023 (12)	1031 (13)	9.0 (6.8)	0.550 (0.017)	0.549 (0.016)	0.003 (0.008)	1431 (77)	1442 (72)	21 (27)
p-value	Group		0.608	0.605	0.945	0.483	0.306	0.548	0.796	0.493	0.466
	Time	3	0.027	0.429	0.552	0.149	0.895	0.324	0.826	0.736	0.732
		6	0.006	0.473	0.074	0.691	0.096	0.385	0.304	0.613	0.672
		12	<0.001	0.083	0.004	0.013	0.008	0.476	0.011	0.010	0.262
	Group	3	0.396	0.602	0.525	0.947	0.868	0.663	0.775	0.405	0.943
	× time	6	0.378	0.304	0.207	0.322	0.822	0.491	0.645	0.987	0.715
		12	0.220	0.711	0.237	0.849	0.896	0.620	0.513	0.838	0.374

Values are estimated mean (SE). $vBMD_{CO}$ = cortical volumetric BMD, CSA_{CO}/CSA_{TOT} = ratio of cortical to total area, SSI = strength-strain index. Side-to-side differences calculated as (non-fractured leg – fractured leg).

IV

PHYSICAL FUNCTION AND LEAN BODY MASS AS PREDICTORS OF BONE LOSS AFTER HIP FRACTURE: A PROSPECTIVE FOLLOW-UP STUDY

by

Suominen T. H., Edgren J., Salpakoski A., Kallinen M., Cervinka T., Rantalainen T., Törmäkangas T., Heinonen A. & Sipilä S. 2020

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RESEARCH ARTICLE Open Access

Physical function and lean body mass as predictors of bone loss after hip fracture: a prospective follow-up study

Tuuli H. Suominen[1*], Johanna Edgren[1], Anu Salpakoski[2], Mauri Kallinen[3,4], Tomas Cervinka[5], Timo Rantalainen[1], Timo Törmäkangas[1], Ari Heinonen[6] and Sarianna Sipilä[1]

Abstract

Background: Predictors of bone deterioration after hip fracture have not been well characterized. The aim of this study was to examine the associations of physical function and lean body mass (LBM) with loss of bone density and strength in older people recovering from a hip fracture.

Methods: A total of 81 over 60-year-old, community-dwelling men and women operated for a hip fracture participated in this 1-year prospective follow-up study. Distal tibia total volumetric bone mineral density ($vBMD_{TOT}$, mg/cm^3) and compressive strength index (BSI, g^2/cm^4) and mid-tibia cortical vBMD ($vBMD_{CO}$, mg/cm^3) and bending strength index (SSI, mm^3) were assessed in both legs by peripheral quantitative computed tomography (pQCT) at baseline (on average 10 weeks after fracture) and at 12 months. At baseline, LBM was measured with a bioimpedance device and physical function with the Short Physical Performance Battery (SPPB) and perceived difficulty in walking outdoors. Robust multivariable linear regression models were used to estimate the associations of physical function and LBM with the change in bone parameters at 12-months.

Results: The mean change in distal tibia $vBMD_{TOT}$ and BSI in both legs ranged from − 0.9 to − 2.5%. The change in mid-tibia $vBMD_{CO}$ and SSI ranged from − 0.5 to − 2.1%. A lower SPPB score, difficulty in walking outdoors and lower LBM predicted greater decline in distal tibia $vBMD_{TOT}$ in both legs. A lower SPPB score and difficulty in walking outdoors were also associated with a greater decline in distal tibia BSI in both legs. At the midshaft site, a lower SPPB score and lower LBM were associated with greater decline in SSI on the fractured side.

Conclusions: Older hip fracture patients with low physical function and lower LBM may be at risk for greater decline in tibia bone properties during the first post-fracture year. Acknowledgement of the risk factors could assist in developing interventions and care to promote bone health and overall recovery.

Trial registration: ISRCTN, ISRCTN53680197. The trial was registered retrospectively but before the recruitment was completed. Registered March 3, 2010.

Keywords: Aging, Bone mineral density, Hip fracture, Lean body mass, Physical function, pQCT

* Correspondence: tuuli.suominen@jyu.fi
[1]Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, PO Box 35, 40014 Jyväskylä, Finland
Full list of author information is available at the end of the article

Background

Substantial decrements in physical function and muscle occur after hip fracture [1, 2], and less than half of these patients recover their pre-fracture level of function [3, 4]. In addition, hip fracture is followed by accelerated and long-term decline in bone structure, density and strength [5–9], especially in the leg on the fractured side [6, 10]. Together with the loss of physical function, bone deterioration increases the risk for a subsequent fracture [11, 12]. Post-hip fracture bone loss can probably be explained in part by disuse, but to date systematic exploration of the factors contributing to post-fracture bone deterioration has been rather scarce.

Low level of physical function is a risk factor for poorer recovery after hip fracture [13]. With the present study population, we have previously shown better recovery of physical function in patients with less difficulty in their post-discharge ability to walk outdoors [13]. A low level of physical function may also prevent effective loading of the bones and could be related to reduced bone-loading physical activity. Moreover, owing to the strong relationship between bone and muscle [14], lower LBM could also contribute to the increase in post-hip fracture bone loss. The positive relationship between bone and muscle can be traced to several biochemical (myokines and osteokines) and biomechanical factors, including gravitational loading on weight-bearing bones and the associated effect of muscle contraction [15], which places the greatest load on bones [14]. In older men, higher LBM has also been associated with better functional recovery after hip fracture [16].

The few studies that have explored the factors contributing to bone loss after hip fracture [2, 17] have not reported either measures of bone strength or outcomes for the leg on the fractured side. The aim of this study was to examine whether physical function, measured with SPPB and perceived difficulty in walking outdoors, and LBM predict the change at 12 months in the bone density and strength of both legs in older men and women recovering from a recent hip fracture.

Methods

Design and participants

This study utilizes data from a randomized controlled trial (ISRCTN53680197) investigating the effects of a yearlong home-based rehabilitation program compared to standard care on mobility recovery among over 60-year-old, ambulatory and community-dwelling older people with a recent hip fracture [18]. The design and recruitment procedure have been reported in detail earlier [19]. Briefly, all men and women who had been operated for a femoral neck or pretrochanteric fracture (ICD code S72.0 or S72.1) in the Central Finland Central Hospital (Jyväskylä, Finland) between 1.3.2008 and 31.12.2010, and fulfilling the inclusion criteria were informed about the study (n = 269). Of these, 161 were interested and further informed on the study. After preliminary assessment of eligibility, 136 persons were invited to the baseline measurements. Patients suffering from severe memory problems (Mini Mental State Examination, MMSE < 18), alcoholism, a severe cardiovascular or pulmonary condition or some other progressive disease, and severe depression (Beck Depression Inventory BDI-II > 29) were excluded from the study. Thereafter, 81 eligible patients participated in the study.

After the baseline measurements, conducted on average 10 weeks post fracture, the participants were randomized into an intervention (n = 40) and a standard care control (n = 41) group using a computer-generated group allocation list generated by a blinded statistician, who was not involved in either the recruitment or data collection process. Blocks of 10, stratified by gender and surgical procedure (internal fixation vs arthroplasty), were used. Follow-up measurements were arranged at 3, 6, and 12 months after the baseline measurements. All assessments were conducted at the research laboratory, and all outcome assessors were blinded to the treatment-group assignment. For the present analyses, data from the rehabilitation and standard care control groups were pooled, since the intervention had no effect on bone properties [10], and only baseline and 12-month follow-up bone data were utilized.

The sample size calculations have been reported in detail before [18, 19]. Briefly, an a priori sample size calculation was performed for the primary outcome, mobility limitation, based on previously published longitudinal data on mobility recovery after a hip fracture [20]. Based on calculations, a minimum of 44 participants were needed in each group (in total 88 participants) to detect the expected difference between the study groups at a level of significance of $\alpha = 0.05$ and $\beta = 0.20$. Sample size was calculated using an online sample size calculator (DSS researcher's toolkit).

Intervention and control condition

All participants received standard care from the hospital. In addition, the intervention group received a year-long, physical rehabilitation program aimed at restoring mobility and physical functional capacity to the pre hip fracture level [18, 19]. The individually tailored program comprised an evaluation and modification of environmental hazards, guidance for safe walking, non-pharmacological pain management, motivational physical activity counselling and a progressive home exercise program. The intervention took place in the participants' homes and included five to six home visits by a physiotherapist. The progressive home exercise program comprised strengthening exercises for the

lower limb muscles using resistance bands, balance training in the standing position, stretching, and functional exercises including walking, reaching, turning in different directions and stair climbing [10, 18].

Peripheral quantitative computed tomography (pQCT)

Bone scans from the distal tibia (5% of measured tibial length proximal to the distal end plate) and tibial shaft (55%) of both legs were obtained by pQCT (XCT-2000, Stratec Medizintechnik, Pforzheim, Germany) according to methods described earlier [10]. The pQCT scans were analyzed with an automated threshold-free cortical bone detection method [the outer boundary detection and subsequent shrinking (OBS) procedure, OBS cortical bone detection 2.1] [21, 22]. The outcome variables for the distal tibia were total volumetric bone mineral density ($vBMD_{TOT}$, mg/cm^3) and compressive bone strength index (BSI, $g^2/cm^4 = vBMD_{TOT}^2 \times CSA_{TOT}$) [8, 9]. For the midshaft site, the variables were cortical vBMD ($vBMD_{CO}$) and a strength-strain index (SSI, mm^3; density-weighted polar section modulus) reflecting the bone's resistance to bending and torsional loads. The root mean square coefficient of variation (CV_{RMS}) for the BMD and strength index measurements in our laboratory ranges from 0.4 to 1.6% [23].

Physical function

Physical function at baseline was measured using the Short Physical Performance Battery (SPPB) test, which includes habitual walking speed, chair rise and standing balance tests [24]. A higher score (range, 0–12) indicates better performance. Perceived difficulty in walking outdoors was assessed by a questionnaire with the following response categories: 1) no difficulties, 2) some difficulties, 3) a great deal of difficulties, 4) manage only with help, and 5) unable to manage even with help.

Lean body mass

Lean body mass (kg) was assessed with a bioimpedance device with eight polar electrodes (BC-418; TANITA, Tokyo, Japan). Participants were instructed to avoid caffeine for 2 h, alcohol for 36 h and physical exercise for 24 h before testing.

Health, fracture status and anthropometry

The presence of chronic conditions, use of prescription medications, fracture date and status, and type and date of surgery were assessed by means of a pre-structured questionnaire, current prescriptions and medical records and confirmed in a medical examination performed by a research nurse and a physician. Contraindications for the physical performance assessments were evaluated according to ACSM guidelines [25]. Body height and weight were measured using standard procedures, and body mass index was calculated as body weight divided by height squared (kg/m^2). Fat percentage was assessed with bioimpedance device. Serum concentrations of 25-hydroxyvitamin D (25OHD, nmol/L) and parathyroid hormone (PTH, ng/L) were determined according to methods described earlier [10]. Smoking status was assessed by questionnaire and categorized as current, former and never smokers.

Statistical analysis

Mean values and standard deviations (SD) were calculated using standard procedures. To alleviate problems resulting from extreme outliers, we used the robust linear regression approach [26] to estimate the associations of the predictor variables with each dependent variable. The mean percentage changes in vBMD and the bone strength indices, used as outcome variables, were calculated as [(follow-up − baseline)/baseline × 100]. Baseline LBM, SPPB score and ability to walk outdoors were entered in the models at the same time as predictors. The SPPB scores were recoded into a single binary variable: 0) high performance (score ≥ 7) or 1) low performance (score < 7). A score below 7 indicates a high risk for disability [27]. The categories of perceived difficulty in walking outdoors were recoded as 0) major difficulties or unable (categories 3–5), or 1) no difficulties or minor difficulties (categories 1–2). Predictive mean matching of the 'mice' package [28] in the R programming environment was used to impute missing values in LBM for three subjects. The models were adjusted for potential confounders: age, gender, surgical procedure (internal fixation vs hemiarthroplasty vs total arthroplasty), number of chronic diseases and use of bisphosphonate medication (yes/no) at baseline. The study group was not included in the models, as no differences were observed in baseline characteristics between the groups and the intervention had no effect on bone properties [10]. The main reasons for missing bone data were inability to perform the measurements, inaccurate positioning of the leg, a technically invalid pQCT scan, substantial movement artifacts, and metal in tissues in the scanned region. For the distal tibia, a total of 154 valid scans were obtained at baseline, and 130 at 12 months. For the midshaft site, the corresponding numbers were 156 and 130. Descriptive analyses were performed using SPSS 24.0 software (IBM, NY, USA) and the robust linear regression models were analyzed using R version 3.5.1 (R core team, Vienna, Austria) with the significance level set at 5%. The study power, calculated for the main outcome, mobility limitation, was 78%.

Results

Baseline characteristics of the participants are shown in Table 1. During the 12-month study, three participants dropped out for personal reasons, and one participant

Table 1 Baseline characteristics of the participants

	n	Mean (SD) or *n* (%)
Age, years	81	80.0 (7.1)
Women, *n* (%)	81	63 (78)
Height, cm	80	161 (9)
Weight, kg	81	65.8 (11.5)
Body mass index, kg/m^2	80	25.5 (3.8)
Body fat, %	76	31.3 (6.5)
Lean body mass, kg	76	44.5 (8.4)
Smoking, n (%)	81	
Never		64 (79)
Former		10 (12)
Current		7 (9)
Number of chronic diseases	81	3 (2)
Current bisphosphonate use, *n* (%)	81	16 (20)
Serum-25OHD, nmol/L	68	55 (23)
Serum-PTH, ng/L	68	49 (23)
Time since fracture (days)	81	70 (28)
Site of fracture, n (%)	81	
Femoral neck		52 (64)
Pertrochanteric		29 (36)
Type of surgery, *n* (%)	81	
Internal fixation		38 (47)
Hemiarthroplasty		33 (41)
Total arthroplasty		10 (12)
Physical function		
SPPB score (range, 0–12)	81	6.2 (2.4)
SPPB score < 7, *n* (%)		42 (52)
Walking outdoors, *n* (%)	81	
No difficulties		12 (15)
Some difficulties		38 (47)
Great deal of difficulties		13 (16)
Manage only with help		17 (21)
Unable to manage even with help		1 (1)
Distal tibia		
$vBMD_{TOT\_fractured\ leg}$ (mg/cm^3)	76	215 (52)
$BSI_{fractured\ leg}$ (g^2/cm^4)	76	0.50 (0.25)
$vBMD_{TOT\_non\text{-}fractured\ leg}$ (mg/cm^3)	78	218 (52)
$BSI_{non\text{-}fractured\ leg}$ (g^2/cm^4)	78	0.51 (0.25)
Tibial midshaft		
$vBMD_{CO\_fractured\ leg}$ (mg/cm^3)	78	1043 (71)
$SSI_{\_fractured\ leg}$ (mm^3)	78	1493 (453)
$vBMD_{CO\_non\text{-}fractured\ leg}$ (mg/cm^3)	78	1045 (78)
$SSI_{\_non\text{-}fractured\ leg}$ (mm^3)	78	1516 (450)

SPPB Short Physical Performance Battery, $vBMD_{TOT}$ Total volumetric bone mineral density, *BSI* Compressive bone strength index, $vBMD_{CO}$ Cortical vBMD, *SSI* Strength-strain index

died unrelated to the research procedures. The mean change from baseline to 12 months in distal tibia $vBMD_{TOT}$ was − 1.5 (SD 4.6) % on the fractured and − 0.9 (3.7) % on the non-fractured side. The corresponding changes for BSI were − 2.1 (8.8) % and − 2.5 (7.0) %, respectively. At the midshaft site, the mean change in $vBMD_{CO}$ was − 1.3 (2.3) % on the fractured and − 0.5 (1.6) % on the non-fractured side. The corresponding changes for SSI were − 2.1 (4.4) % and − 1.5 (3.4) %.

In the adjusted multivariable regression analyses, a lower SPPB score, difficulty in walking outdoors and lower LBM at baseline predicted greater decline in distal tibia $vBMD_{TOT}$ both on the fractured and non-fractured sides (Table 2). A lower SPPB score and difficulty in walking outdoors were also predictive of a greater decline in the distal tibia BSI on both sides. At the midshaft site, a lower SPPB score and lower LBM were associated with a greater decline in the SSI on the fractured side.

Discussion

In this 12-month follow-up study of older, community-dwelling men and women operated for a hip fracture, we found that lower physical function and lower LBM predicted greater decline in distal tibia bone density during the year following the fracture. Lower physical function was also associated with a greater decline in distal tibia bone strength. At the midshaft site, a lower SPPB score and lower LBM were predictive of a greater decline in bone strength on the fractured side.

Despite the large body of research on the factors contributing accelerated bone loss in aging people, very few have been conducted on hip fracture patients [2, 17] and none have examined potential predictors of the changes in bone properties over time. As in our previous studies [6, 10], bone deterioration was more pronounced in the leg on the fractured side, a finding which may partly be explained by disuse. No between-side differences in the predictors were, however, found except for mid-tibia SSI. At the midshaft site, a lower SPPB score and lower LBM were predictive of greater decline in the SSI on the fractured side only. Neither the decline in SSI on the non-fractured side nor the decline in cortical vBMD on both sides was associated with any of the factors studied, suggesting that the mid-tibia may not be equally sensitive to differences in the predictors used.

In the present study, a lower SPPB score (under 7) and major difficulty in the ability to walk outdoors predicted greater deterioration in distal tibia volumetric bone density and strength. This is in line with our previous findings indicating better functional recovery in patients with better function [13] and supports our hypothesis of better bone recovery in patients with a better capacity to load their bones. In old age, walking outdoors has also been associated with a greater amount of objectively

Table 2 Multiple linear regression models predicting changes in distal tibia and tibial mid-shaft bone characteristics

	Fractured side				Non-fractured side			
Distal tibia	**$vBMD_{TOT}$** ($n = 58$)		**BSI** ($n = 58$)		**$vBMD_{TOT}$** ($n = 59$)		**BSI** ($n = 56$)	
	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*
Lean body mass	.152 (0.06)	.010	.136 (0.12)	.258	.151 (0.06)	.010	.152 (0.10)	.126
SPPB[a]	−1.44 (0.64)	.028	−3.09 (1.33)	.023	−1.34 (0.64)	.040	−3.06 (1.11)	.007
Walking outdoors[b]	−2.05 (0.74)	.009	−3.62 (1.53)	.024	−2.67 (0.74)	<.001	−5.69 (1.28)	<.001
	$R^2 = .236$	<.001	$R^2 = .182$	.006	$R^2 = .363$	<.001	$R^2 = .428$	<.001
Tibial midshaft	**$vBMD_{CO}$** ($n = 57$)		**SSI** ($n = 58$)		**$vBMD_{CO}$** ($n = 58$)		**SSI** ($n = 57$)	
	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*	B (SE)	*p*
Lean body mass	−.025 (0.04)	.531	.171 (0.08)	.042	−.004 (0.04)	.910	.129 (0.07)	.067
SPPB[a]	−.538 (0.46)	.247	−2.03 (0.93)	.034	−.193 (0.43)	.655	−.062 (0.78)	.938
Walking outdoors[b]	−.371 (0.54)	.485	−0.60 (1.08)	.578	−.356 (0.50)	.476	−.343 (0.90)	.711
	$R^2 = .119$	.286	$R^2 = .247$	.023	$R^2 = .015$	.566	$R^2 = .157$	.421

The models were adjusted for age, sex, surgical procedure, number of chronic diseases and use of bisphosphonates at baseline. Sample size reduction due to weighting ranged from 5 to 10%

$vBMD_{TOT}$ Total volumetric bone mineral density, *BSI* Compressive bone strength index, *$vBMD_{CO}$* Cortical vBMD, *SSI* Strength-strain index, *SPPB* Short Physical Performance Battery

[a]0) high performance (score ≥ 7), 1) low performance (score < 7)

[b]0) without difficulties/minor difficulty 1) major difficulty/unable

measured physical activity [29]. Furthermore, our results are in line with previous studies suggesting better post-fracture functional recovery [16] and reduced age-related bone loss [30] for men with higher LBM. Moreover, in older, often frail and undernourished, hip fracture patients, higher LBM may also reflect better resources to cope with a prolonged catabolic state and the hip fracture-related stresses.

This study has its limitations. The study reports the results of a secondary analysis of an RCT, and the observational design demonstrates only associations, not causal relationships. Because of missing data and a relatively small sample size, we had to limit the number of possible confounders included in the analyses. Down-weighting the influence of outliers in the regression analyses further reduced the sample size but yielded more reliable regression coefficients. Moreover, the participants were community-living, and therefore the results may not be generalizable to all hip fracture patients. Furthermore, DXA or MRI would have provided more accurate LBM results. Finally, constraints related to the imaging method used, such as scan resolution, partial volume effect and beam hardening should be considered when interpreting the results. The strengths of the study include a population-based clinical study sample, a 3D imaging modality to assess changes in volumetric bone mineral density and estimated strength in the leg on the fractured side, and a longitudinal follow-up of sufficient length to detect changes in bone properties.

Conclusions

In conclusion, low physical function and lower LBM may increase the risk for accelerated bone deterioration in older hip fracture patients. Attention should be paid to patients at greater risk for poorer recovery, and more effective, multidimensional and individualized interventions and care should be provided to promote bone health and overall recovery. Due to limited possibilities to prevent bone deterioration after hip fracture, attention should be paid to physical function, muscle mass preservation and fall prevention before as well as after fracture occurrence.

Abbreviations

25OHD: 25-hydroxyvitamin D; BSI: Compressive bone strength index; LBM: Lean body mass; OBS: Outer boundary detection and subsequent shrinking procedure; pQCT: Peripheral quantitative computed tomography; PTH: Parathyroid hormone; SPPB: Short Physical Performance Battery; SSI: Strength-strain index; $vBMD_{CO}$: Cortical volumetric bone mineral density; $vBMD_{TOT}$: Total volumetric bone mineral density

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CONSORT statement
This study adheres the CONSORT guidelines.

Authors' contributions
Study design: SS, AH, MK. Study conduct: SS, JE, AS, MK. Data collection: SS, JE, AS, MK. Data analysis: THS, TC, TT. Data interpretation: THS, TR, TT, AH, SS. Drafting manuscript: THS. Revising manuscript content: THS, JE, AS, MK, TC, TR, TT, AH, SS. Approving final version of manuscript: THS, JE, AS, MK, TC, TR, TT, AH, SS. THS, TC, TT, SS take responsibility for the integrity of the data analysis.

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Availability of data and materials
The datasets used and analyzed during the current study are available from SS on reasonable request.

Ethics approval and consent to participate
All participants gave their written informed consent and permission to review their medical records prior to participation in the study. The study was approved by the Ethics Committee of the Central Finland Health Care District (Dnro56/2007) and conformed with the principles of the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Gerontology Research Center, Faculty of Sport and Health Sciences, University of Jyväskylä, PO Box 35, 40014 Jyväskylä, Finland. [2]Rehabilitation Center Peurunka, Laukaa, Finland. [3]Department of Physical and Rehabilitation Medicine, Central Finland Health Care District, Central Finland Central Hospital, Jyväskylä, Finland. [4]Center for Life Course Health Research, University of Oulu, Oulu, Finland. [5]Satakunta University of Applied Sciences, Pori, Finland. [6]Faculty of Sport and Health Sciences, University of Jyväskylä, Jyväskylä, Finland.

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