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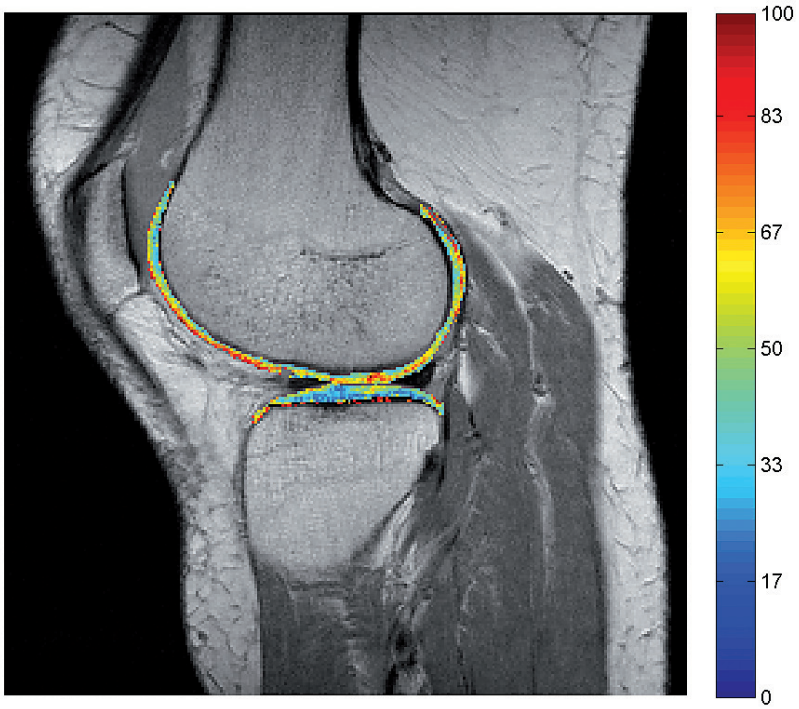
Juhani Multanen

Exercise for Bone and Cartilage in Postmenopausal Women with Mild Knee Osteoarthritis



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UNIVERSITY OF JYVÄSKYLÄ

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ABSTRACT

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The purpose of this study was to investigate the effects of high-impact exercise on bone mineral mass and strength, and on knee cartilage composition in postmenopausal women with mild knee osteoarthritis (OA). In addition, the association between knee OA and femoral neck bone structural characteristics in women with mild knee radiographic OA and those without radiographic knee OA was studied. Also, the reproducibility of measuring human knee joint cartilage by the delayed gadolinium-enhanced MRI (dGEMRIC) technique was determined in healthy asymptomatic subjects.

Data from a 12-month randomized controlled trial (RCT) was used to assess the effects of exercise on bones and cartilages. The training intervention comprised 80 postmenopausal women with mild knee OA. The primary outcomes were bone mineral mass and strength, and the biochemical composition of knee cartilage as assessed by quantitative MRI measures: dGEMRIC and T2 relaxation time. Physical performance-related risk factors of falling were also evaluated. Data assembled from an additional sample of postmenopausal women with no knee symptoms (n = 12) and from the baseline measures of the postmenopausal women with mild knee OA were used in the cross-sectional association study. Prior to RCT, a test-retest study was conducted in healthy subjects (n = 10) to assess the reproducibility of dGEMRIC.

The dGEMRIC technique showed good day-to-day reproducibility for the different knee cartilage regions. In the association study, femoral neck bone characteristics were significantly higher with higher grades in radiographic knee OA, indicating an inverse relationship between OA and osteoporosis (OP). The exercise program increased femoral neck bone mineral mass and strength. Exercise also had positive effects on physical performance-related risk factors for falls and exercise participation was well endured. However, the exercise had no effect on knee cartilage composition. To conclude, progressively implemented high-impact training is a safe and feasible exercise modality in the prevention of OP and physical performance–related risk factors for falls in postmenopausal women with mild knee OA.

Keywords: exercise, osteoarthritis, postmenopausal women, cartilage, bone

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Jyväskylä, February 2016
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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which will be referred to in the text by their Roman numerals.

I Multanen J, Rauvala E, Lammentausta E, Ojala R, Kiviranta I, Häkkinen A, Nieminen MT, Heinonen A. Reproducibility of Imaging Human Knee Cartilage by Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) at 1.5 Tesla. Osteoarthritis and Cartilage 2009;17:559-564.

II Multanen J, Heinonen A, Häkkinen A, Kautiainen H, Kujala U, Lammentausta E, Jämsä T, Kiviranta I, Nieminen MT. Bone and Cartilage Characteristics in Postmenopausal Women with Mild Knee Radiographic Osteoarthritis and Those without Radiographic Osteoarthritis. Journal of Musculoskeletal and Neuronal Interactions 2015; 15(1):69-77.

III Multanen J, Nieminen MT, Häkkinen A, Kujala UM, Jämsä T, Kautiainen H, Lammentausta E, Ahola R, Selänne H, Ojala R, Kiviranta I, Heinonen A. Effects of High-Impact Training on Bone and Articular Cartilage: 12-Month Randomized Controlled Quantitative MRI Study. Journal of Bone and Mineral Research 2014;29(1):192-201.

IV Multanen J, Rantalainen T, Kautiainen H, Ahola R, Jämsä J, Nieminen MT, Lammentausta E, Häkkinen A, Kiviranta I, Heinonen A. Effect of Progressive High-Impact Exercise on Femoral Neck Structural Strength in Postmenopausal Women with Mild Knee Osteoarthritis: A 12-Month RCT. *Submitted to Osteoporosis International.*

ABBREVIATIONS AND SYMBOLS

aBMD	Areal bone mineral density
AHA	Advanced hip analysis
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
BMU	Basic multicellular unit
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BW	Body weight
CI	Confidence interval
COMP	Cartilage oligometric matrix protein
CSA	Cross-sectional area
CSMI	Cross-sectional moment of inertia
CT	Computed tomography
CV	Coefficient of variation
CV_{RMS}	Coefficient of variation of the root-mean-square
dGEMRIC	Delayed gadolinium-enhanced magnetic resonance imaging of cartilage
DIS_{Log}	Daily impact score
DIS_{Total}	Total physical activity loading index
DXA	Dual-energy x-ray absorptiometry
ECM	Extra cellular matrix
ERT	Estrogen replacement therapy
ES	Effect size
ETL	Echo train length
FOV	Field of view
g	Gravity
GAG	Glycosaminoglycan
$Gd\text{-}DTPA^{2-}$	Gadolinium embedded diethylene triaminopentaacetate acid
GRF	Ground reaction force
HA	Hyaluronan
HRQoL	Health-related quality of life
HRT	Hormone replacement therapy
HSA	Hip structural analysis
ICC	Intra-class correlation coefficient
IQR	Interquartile range
K/L	Kellgren and Lawrence
KS	Keratin sulfate
MANOVA	Multivariate analysis of variance
MET	Metabolic equivalent task
mL	Millilitre

mm	Millimeter
mM	Millimolar
MRI	Magnetic resonance imaging
ms	Millisecond
OA	Osteoarthritis
OP	Osteoporosis
OVX	Ovarectomy
PA	Physical activity
PG	Proteoglycan
pQCT	Peripheral quantitative computed tomography
PUFA	Polyunsaturated fatty acids
PTH	Parathyroid hormone
QCT	Quantitative computed tomography
qMRI	Quantitative magnetic resonance imaging
QUS	Quantitative ultrasound
RAND-36	Health-related quality of life survey instrument
ROI	Region of interest
RCT	Randomized controlled trial
SD	Standard deviation
SMD	Standardized mean difference
T	Tesla
TE	Echo time
TI	Inversion time
TR	Repetition time
TGF-β1	Transforming growth factor-beta 1
T1	Spin-lattice relaxation time
T2	Spin-spin relaxation time
UET	Ultrashort echo time
vBMD	Volumetric bone mineral density
vQCT	Volumetric quantitative computed tomography
VO_{2max}	Maximal oxygen uptake
W	Width (of the proximal femur), or watt as the unit of power
WHO	World Health Organization
WOMAC	Western Ontario and McMaster University Osteoarthritis Index
X-ray	Röntgen radiation / Radiography
Z	Section modulus

CONTENTS

1 INTRODUCTION

Osteoarthritis (OA) and osteoporosis (OP) are two common diseases that are closely associated with aging, morbidity and disability (Dequeker et al. 2003). Osteoporosis, literally meaning "porous bone" increases the risk of sudden and unexpected bone fracture as a consequence of lowered bone mass and strength. Postmenopausal OP is of particular concern, since OP is more common in women than men (Melton et al. 1992) and since the prevalence of OP increases with age, especially after the age of 50 years. For instance, a recent study on the epidemiology of OP in the United States found a prevalence of 15% among women aged 50 and over, and a prevalence of 35% among women aged 80 and over (Wright et al. 2014). The incidence of hip fracture, the most serious outcome of OP, is highest for women in the Nordic countries (Wade et al. 2012). Likewise, OA is a common condition, particularly after menopause, when the disease becomes more prevalent, severe and generalized in women than in men (Wluka et al. 2000, Pereira et al. 2011). Knee OA in particular is associated with severe disability, owing to the weight-bearing function of the knee and the large range of movements it performs. Determining the prevalence of OA, however, is not a straight-forward matter due the inconsistent relationship between clinical symptoms and radiographic findings (Mandl 2007). For example, in their meta-analysis, Pereira et al. (2011), found that radiographic assessment yields higher estimates (39%) of the overall prevalence of knee OA in women than assessments based on clinical symptoms (16%) or self-reports (13%) (Pereira et al. 2011). In Finnish women, the prevalence of clinically diagnosed knee OA is 0.4% in the age group of 30 to 44 years, rising to 36% in the age group of 85 years and older (Arokoski et al. 2007). With the general aging of the population, OA and OP present a serious and growing public health concern, which is why more efficient population level interventions for preventing and treating these diseases are needed.

It is well established that regular and sufficient bone exercise loading is vital for bone health, and that high-impact loading is the most osteogenic exercise for this purpose (Sievänen 2012). Earlier, clinicians and researchers argued that mature articular cartilage, the key factor in early pathological

changes in OA, is an inert bearing surface and not capable of repairing damage (Buckwalter & Mankin 1998). This gradually led to the view that OA was a wear and tear disease, where mechanical loading from exercise could further damage joints. However, as our understanding of the articular cartilage capacity to restore and remodel itself has increased over the last couple of decades, there has been a shift in the view of the value of exercise in preventing and treating knee OA (Shrier 2004). In fact, there is an increasing body of evidence to show that exercise is beneficial in relieving OA symptoms and improving physical function (Uthman et al. 2013, Juhl et al. 2014, Fransen et al. 2015). In addition, the Osteoarthritis Research Society International (OARSI) has recently recommended exercise, such as strength training together with weight management, as a key treatment modality for the non-surgical management of knee OA (McAlindon et al. 2014). Yet, literature continues to be lacking on the effects of exercise on articular cartilage in OA, with the exception of some earlier animal models with artificially induced OA or sedentary lifestyle (Kiviranta et al. 1992, Otterness et al. 1998, Haapala et al. 1999), and one human trial with patients at high risk for OA (Roos & Dahlberg 2005). The results of those studies suggest that cartilage has potential for exercise adaptation via increase in its proteoglycan content. Since nowadays, with advanced imaging techniques, it is possible to detect bone and cartilage properties in detail, some clinical questions have arisen with regard to OP and OA. First, as OA and OP often coexist in middle-aged and elderly women, could persons who have frail cartilage and who are at risk for OP benefit from the same bone-favorable exercise? Secondly, as high intensity loading and certain types of sport participation have been associated with joint injury and OA development (Kujala et al. 1995, Bennell et al. 2011), does high-impact loading have controversial effects on articular cartilage and bone? To be able to answer these questions, there is a need for an experimental study to look the effects of long-term exposure to joint loading on both bone and cartilage properties.

The main purpose of this doctoral thesis was to investigate the effects of a 12-month progressive high-impact exercise program on bone strength and structure, knee cartilage biochemical composition and physical function in postmenopausal women with mild knee OA. To the best of our knowledge, no randomized controlled trial has been performed in OA subjects to examine the effects of high-impact physical activity on cartilage properties, let alone both on cartilage and bone health. An improved understanding of the effects of high-intensity joint loading on cartilage and bone structures will have practical value for physicians, physiotherapists and other health care professionals in prescribing appropriate exercise programs for subjects with and without OA who may be at risk for OP. Another purpose of this thesis was to determine the reproducibility of measuring human articular cartilage in the knee joint by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), which was used to assess the effects of exercise on knee cartilage. This thesis also investigated bone and cartilage characteristics in postmenopausal women with mild knee radiographic OA and those without radiographic OA.

2 REVIEW OF THE LITERATURE

2.1 Bones and articular cartilages

The human skeleton is composed of cartilage and bones. In adult human body three types of cartilage can be distinguished: elastic, hyaline and fibrous cartilage (Gartner & Hiatt 2011, Cole 2011). In this doctoral thesis, where volitional human movements of the limbs are discussed, the term "articular cartilage" or simply "cartilage" indicates hyaline cartilage, which typically is found in a diarthrodial synovial joint, enabling smooth gliding movements within the articulating bones. In addition to bones and articular cartilage, a fibrous articular capsule passing between two bones and a synovial membrane collectively form the synovial joint. A synovial membrane lines the inner surface of the capsule and covers all non-articular surfaces within the capsule. The synovial membrane secretes synovial fluid into the joint space enclosed by the capsule, and serves to lubricate and nourish the cartilage (Palastanga & Soames 2012).

2.1.1 Structure and function

Bone

The skeleton has both mechanical and physiological functions. Bones provide the body with a rigid and light frame for efficient locomotion (Frost 2003). In addition, bones give protection to vital organs. Physiologically, bones help maintain mineral homeostasis by acting as a site for calcium storage and forming blood cells in the bone marrow (Guyton & Hall 2006). Additionally, bones have a role as an endocrine organ, by producing the hormones which will have an outcome effect on vitamin D hydroxylation and phosphorous excretion (Fukumoto & Martin 2009). The skeleton can be divided into the axial and the appendicular (also called peripheral) skeleton. The axial skeleton comprises the bones of the skull, the vertebral column and the rib gage. The appendicular skeleton comprises the bones of the upper and lower extremities. The

macrostructure of long bones, such as the tibia and femur, is divided into epiphysis, metaphysis and diaphysis (Figure 1).

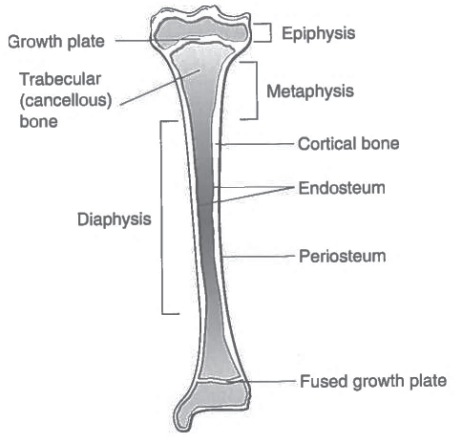


FIGURE 1 Schematic view of a growing long bone. Adapted from Khan et al. (2001a).

Bone tissue is organized into trabecular (also called cancelleous or spongy) and cortical (compact or dense) bone. Trabecular bone, which is highly porous in structure, is found in the axial skeleton and in the epiphysis and metaphysis of the long bones. Trabecular bone acts as load-bearing tissue. It also transfers loads across joints, supports compressive loads and acts as a shock absorber. The strength of trabecular bone is influenced by its microarchitecture, i.e., the volume, number, thickness, orientation, connectivity, perforation and spacing of the trabeculae (Borah & Dufresne 2006). Cortical bone, which is found in the shafts of long bones, is highly calcified, accounting for approximately 80% of the skeletal mass of the human body. The strength of cortical bone is determined by its thickness and porosity (Chappard 2006). Both the epiphysis and metaphysis also have a thin shell or cortical bone surrounding the trabecular compartment. The inner surface of cortical bone is called the endosteum and it faces the bone marrow. The endosteum is metabolically active and heavily involved in bone formation and resorption. The outer surface of cortical bone is called the periosteum. It is a two-layer structure contributing, for example, to appositional growth during bone development and increasing the diameters of the long bones with aging (Khan et al. 2001a).

Bone tissue consists of inorganic (~60 - 70% by weight) and organic (~20 - 30%) materials and water (~5 - 10%). The inorganic phase comprises mainly an impure form of hydroxyapatite, a naturally occurring calcium phosphate. The organic phase is composed predominantly (98%) of type I collagen and a variety of noncollagenous proteins. Minerals give bone its stiffness, while collagen provides flexibility. The rest of bone is made up of cells: osteoblasts, osteocytes and osteoclasts. These specialized bone cells are involved in the regulation of bone metabolism, by responding to multiple environmental

signals, including chemical, mechanical, electrical, and magnetic stimuli (Khan et al. 2001a).

Bone is constantly being turned over. There are two processes of bone turnover; modeling and remodeling. Modeling is the process that changes the shape, size and geometry of bone in childhood and adolescence, and also in adult life, in response to changes in loading patterns. Modeling involves deposition of a collagen matrix and mineralization of this matrix without previous bone resorption (Forwood 2001, Dempster 2006). Remodeling, however, is a continuous process that enables bone to repair damage, maintain its structural integrity and perform mineral homeostasis. Bone remodeling is carried out by a coordinated group of different cell types, called basic multicellular units (BMU) (Dempster 2006). In the resting state, no resorption or bone formation takes place. During activation, the resting bone cells, osteocytes, sense any mechanical changes and remodeling decreases or increases accordingly. Osteoclast precursors transform into osteoclasts, i.e., cells that resorb bone. In the reversal phase, osteoclasts undergo apoptosis and resorption stops. Any collagen uncleared by osteoclasts is removed by specific mononuclear cells, which then deposit a thin layer of proteoglycans to form the cement line. During the formation phase, new bone is formed by osteoblasts. This biologically coupled activation → resorption → formation sequence lasts about 4 months (Frost 1997). Remodeling can remove or retain bone mass and strength, but apparently does not increase these without the help of pharmacological agents (Frost 1992).

Articular cartilage

Articular cartilage is aneural and avascular tissue that covers the ends of articulating bones in the synovial joint. The main functions of articular cartilage are to resist tensile, shear and compressive forces, optimally distribute joint loading to the underlying bone, and to provide an almost frictionless gliding surface for the articulating bones (Wong & Carter 2003, Buckwalter et al. 2005). Macroscopically, articular cartilage appears as a smooth, homogenous tissue approximately 2 to 5 mm thick (Figure 2).

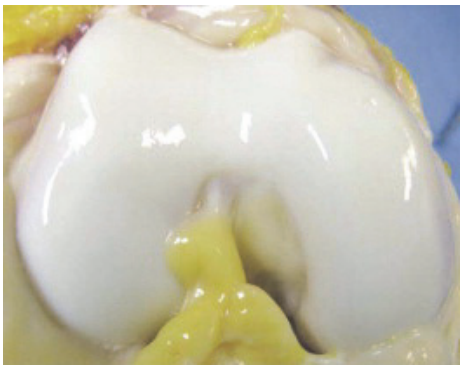


FIGURE 2 Gross image of articular cartilage on the femoral condyle of a healthy 20-year-old female. This image displays the smooth, homogenous surface appearance of normal articular cartilage. From Henry et al. (2012) with permission of Elsevier.

In normal articular cartilage, there is only one cell type, chondrocytes, which account for little of the volume of the tissue, about 1% in adult human cartilage (Buckwalter & Mankin 1998). Individual chondrocytes, which are metabolically active, synthesize type II collagen, large aggregating proteoglycans (PG) and specific noncollagenous proteins (Buckwalter & Mankin 1998). Although chondrocytes are capable of synthesizing molecules for cartilage maintenance, owing to its low cell density adult cartilage does not have the capacity to repair severe damage resulting from injury or disease (Mow et al. 1992). The main solid constituent of the articular cartilage, also known as the extracellular matrix (ECM), includes collagen fibers and proteoglycans. The collagen fibers, mainly type II collagen, are oriented according to the loading stresses placed on the cartilage, and form a three dimensional fibrous collagen network. Three layers can be distinguished in mature articular cartilage according to the depth of the tissue (Mow et al. 1992). In the superficial zone (tangential zone), the collagen fibers are oriented in parallel to the cartilage surface. In the intermediate zone (transitional zone), the collagen fibers are more randomly organized, changing from parallel to perpendicular to the surface in the deeper cartilage. In the deep zone (radial zone), the collagen fibers are perpendicular to the cartilage surface, anchoring to the subchondral bone through the tidemark and calcified cartilage (Mow et al. 1990). In general, collagen content decreases from the articular surface towards the deep cartilage (Venn & Maroudas 1977).

The proteoglycans (PG) are the other macromolecules of cartilage. These consist of a protein core to which a large number covalently attached glycosaminoglycan (GAG) chains are attached. The GAG chains stick out from the protein core like the bristles on a bottle brush (Meisenberg & Simmons 2012) (Figure 3). The negatively charged GAGs attract cation ions, which in turn attract water molecules, increasing the tendency of the tissue to swell (Gartner & Hiatt 2011). This intra-cartilage pressure sets collagen fibers in a state of tension, even in unloaded cartilage. In addition to regulating the movement of

molecules through the matrix, GAG chains attached to PGs enable nearly frictionless movement of articulating surfaces by serving as lubricants (Lu et al. 2004). PG content increases towards the deep cartilage (Kiviranta et al. 1985). Collagen molecules in cartilage have an exceptionally long life-time, extending over 100 years (Verzijl et al. 2000), whereas the half-life for PGs has been calculated to be between 3 and 25 years (Maroudas et al. 1998). The mechanism that controls the balance between ECM degradation and synthesis remains poorly understood, but cytokines with catabolic and anabolic effect appear to have important roles (Buckwalter et al. 2005). In addition of extracellular constituents, cartilage contains solutes, such as nutrients and ions, as well as interstitial water. The majority of the interstitial water is associated with negatively charged PGs and resides in the intrafibrillar space within collagen fibers. Water content is highest in the superficial tissue, decreasing towards deeper tissue (Lemperg et al. 1971, Venn & Maroudas 1977).

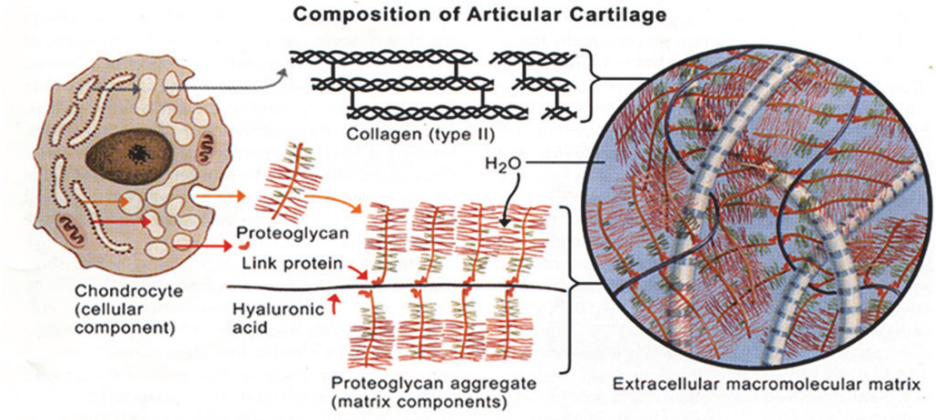


FIGURE 3 Chodrocytes synthesize collagen (structural framework) and hydrophilic proteoglycans, which interact with collagen fibrils to form the hydrated macromolecular matrix of articular cartilage. Adapted from Buckwalter & Martin (1995).

The physical interaction between the collagen network, PGs and interstitial water in articular cartilage is essential in distributing loads to underlying bones and lubricating contact surfaces. The ability of PGs to bind water allows them to swell, while the collagen network restricts this swelling, inducing initial swelling pressure (Mow et al. 1990). When a mechanical load is applied to cartilage, the pressure in the cartilage matrix increases and interstitial fluid begins to flow to minimize the pressure gradients in the tissue. After releasing the load, the PGs expand, causing the pressure gradient to reverse direction. An in vitro study with adult human articular cartilage has shown that the collagen network largely controls the elastic responses, while the viscous response is controlled largely by the hydrated PGs (Bader & Kempson 1994). Regular cyclic loading of the joint is needed to preserve the physiological properties of

cartilage by enhancing cartilage nutrition and moving catabolites from cartilage into the synovial space, and by enhancing the synthesis and rate of turnover of PGs, maintaining cartilage stiffness (Palmoski et al. 1980, Salter 1981, Suwalska 1982, Panush et al. 1986, Arokoski et al. 2000).

Age-related changes in cartilage include thinning and some surface wear (Loeser 2007). Surface wear in tissue is particularly common in load-bearing areas (Meachim 1976). In a cross-sectional study, magnetic resonance imaging (MRI) revealed that increasing age was accompanied by increased cartilage defect severity and prevalence, cartilage thinning, and increased patellar bone volume as well as lateral and medial tibial bone area (Ding et al. 2005). Another MRI study conducted in asymptomatic 22 to 86 year old women showed an age- and depth-related increase in patellar cartilage T2 relaxation time values, which are hypothesized to reflect collagen structure and orientation (Mosher et al. 2004). These findings are thought to indicate that age-related changes in collagen structure begin near the articular surface and progress to the deeper cartilage with advancing age (Mosher et al. 2004). In cartilage the microstructure, aggregan (the large cartilage proteoglycan) fragments appear to accumulate in the matrix due to the low cartilage turnover rate (Verzijl et al. 2000). In addition, changes in the cartilage matrix, such as calcification (Wilkins et al. 1983, Felson et al. 1989), increased lipid content (Bonner et al. 1975), and browning have been associated with the aging process. Browning in the cartilage is probably due to the accumulation of advanced glycation end products (Verzijl et al. 2003). The formation of advanced glycation end products has been associated with increased cartilage stiffness and brittleness, which in turn renders cartilage more prone to failure (Bank et al. 1998). With aging, there is also a decrease in the hydration of the cartilage matrix, with a corresponding increase in compressive stiffness (Sophia Fox et al. 2009).

2.1.2 Pathophysiology; osteoporosis and knee osteoarthritis

Osteoporosis

Osteoporosis is defined as a systematic skeletal disease characterized by low bone mineral mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture (Consensus development conference 1993). The diagnosis of the disease is based on the quantitative assessment of bone mineral density (BMD, g/cm^2). The technique most widely used to assess BMD is based on dual-energy X-ray absorptiometry (DXA) (Kanis et al. 2008a). BMD is derived by dividing the bone mineral content (BMC, g) by the area (cm^2) measured (more detailed DXA information is provided in this thesis section on "assessment of bone and articular cartilage"). The World Health Organization (WHO) defines OP as a condition in which areal BMD (aBMD) is less than -2.5 standard deviations (SD) below peak bone mass (Kanis 1994); that is, a -2.5 T-score, measured in units of -2.5 SD, below that of young Caucasian female, while a T-score between -1.0 and -2.5 is considered to indicate osteopenia. Osteopenia defines those with low bone mass who are likely to develop OP in the future (Kanis et al. 1997). In

postmenopausal women, low bone mineral mass results from either low peak bone mass or increased bone loss during and after menopause. Although the diagnosis of OP relies on the quantitative assessment of BMD, the clinical significance of the disease pertains to the fractures that arise. Common sites for osteoporotic fracture are the spine, hip and distal forearm (Borah & Dufresne 2006). Despite the fact that the fracture risk increases with decreasing levels of BMD, many patients with OP will not sustain a fracture, while most fractures in the general population occur in subjects without OP (Siris et al. 2001, Sanders et al. 2006, Järvinen et al. 2015b).

Risk factors and treatment

In addition to low BMD, age, genetics, environmental factors and chronic disease are the most important risk factors for lowered bone mass and osteoportic fractures (Kanis 2002, Weppner & Alvero 2016). With aging, each decade after 40 years is associated with a fivefold increased risk for OP. Genetically, ethnicity plays a role; for example, Caucasian and Asians are affected more often than blacks. Also, females are affected more often than males, and family history of fragilty fractures increases the risk for OP. Environmental factors, such as poor nutrition, calcium deficiency, physical inactivity, tobacco and alcohol use, high caffeine intake, traumatic injury and some medications also increase the risk for OP. Moreover, some chronic diseases, such as estrogen and androgen deficiency, hyperthyroidism, inflammatory bowel diseases, malabsorption, diabetes mellitus and hypercortisolism increase the risk for OP (Papaioannou et al. 2009, Karinkanta et al. 2010, Weppner & Alvero 2016). In addition to these risk factors, there are many others, and some algorithms for assessing fracture risk on the basis of clinical risk factors in the absence of BMD measurements have recently been made available (Cummins et al. 2011). The first such algorithm to be developed was FRAX®, a tool for outpatient care with the aim identifying patients at increased fracture risk and bringing them into care (Kanis et al. 2008b). FRAX® calculates the ten-year risk for osteoporotic fractures and is country-specific, as fracture rates vary considerably in different countries (Kanis et al. 2002). However, one limitation of FRAX® is that for several of risk factors, such as information on falls or the magnitude of exposure of alcohol or smoking is not taken into account (Collins & Michaelsson 2012). FRAX®-based screening and subsequent treatment recommendations have been also accused of promoting overdiagnosis and misdirection of pharmaceutical resources (Järvinen et al. 2015b). Ideally, the combination of clinical risk factors and BMD provide the highest specifity and sensitivity (Kanis et al. 2007).

The primary goal of OP management is the prevention of fractures. The main strategies for achieving this goal at the population level are to ensure a sufficient intake of calcium and vitamin D, and sufficient physical exercise, smoking cessation and, most importantly, fall prevention (Arokoski et al. 2014). In fact, some researchers consider that the focus in OP should be shifted from fracture prevention to stopping falls (Järvinen et al. 2008), since over 80% of low

trauma fractures occur in people who do not have OP (Stone et al. 2003). In the pharmacological treatment of OP, the first-line therapy is oral bisphonates, which decrease bone resorption by attenuating osteoclast activity. According to the American Association of Clinical Endocrinologists, several other drugs are also used to treat OP, such as selective estrogen receptor modulators (SERs), which are considered to provide the beneficial effects of estrogen without the potentially adverse outcomes, parathyroid hormone, which is an anabolic agent for the treatment of OP, calcitonin, which decreases osteoclast activity, denosumab, which decreases bone resorption by inhibiting osteoclast activity, and hormone replacement therapy (HRT) (Watts et al. 2010). Although there is evidence that pharmacological treatment, and bisphosphonate use in particular, is effective in the prevention of osteoporotic fractures in postmenopausal women (Wells et al. 2008), it should be noted that some drugs for the treatment of OP have been associated with increased risks for serious adverse events. For example, atypical femoral shaft fracures (Odvina et al. 2005, Schilcher et al. 2011, Schilcher et al. 2014, Shane et al. 2014), osteonecrosis of the jaw (Ulmner et al. 2014) and gastrointestinal problems (Reid 2011) have been reported in oral bisphosphonate use.

Knee osteoarthritis

Osteoarthritis (OA), also known as degenerative joint disease or arthritis, is the most common joint disease and is highly associated with age (Felson 2003, Abramson et al. 2006). Although OA can occur in any synovial joint (Buckwalter & Mankin 1998), knees are among the joints most commonly affected by OA (Andrianakos et al. 2006). Knee OA most commonly presents simultaneously in the medial tibiofemoral and patellofemoral compartments (Ledingham et al. 1993, Duncan et al. 2006). In the tibiofemoral compartment, radiography has shown the medial side to be most commonly affected (Ledingham et al. 1993). The interest in OA in this doctoral thesis, unless otherwise specified, is in the tibiofemoral compartment in the knee. It is the topic of the empirical part and has been well characterized in the literature by epidemiological, clinical and intervention studies.

Symptoms and signs

The most common symptoms of knee OA are pain, stiffness, swelling, and reduced range of motion. Knee pain is the most common complaint, and the main reason why patients seek medical care. Knee pain intensity can fluctuate, but over the years most patients with knee OA experience increased pain (Dieppe et al. 2000). Typically knee pain occurs during weight-bearing activities, but as OA progresses, the pain may become more persistent and also occur at rest and during the night. The correlation between knee pain and the degree of structural radiographic changes is poor (Creamer & Hochberg 1997, Hannan et al. 2000, Bedson & Croft 2008), although joints with severe radiographic change are more likely to be painful (O'Reilly & Doherty 2003). Morning stiffness or slowness after inactivity is generally transient compared to the more prolonged

inflammatory joint conditions. Fluid in the joint may accumulate, causing a swollen knee joint. Joint swelling usually occurs after a long period of excessive activity. As the OA progresses, limited movement of the joint and crepitus may occur due to osteophyte formation, bone remodeling and capsular thickening. Physical function impairments may also include reduced muscle function and proprioception, laxity or instability of the knee joint, and weakened aerobic fitness and postural control (Bennell et al. 2011). In addition, joint tenderness and warmth may be found during clinical assessment, suggesting that pain and synovitis are of capsular origin (O'Reilly & Doherty 2003).

Pathogenesis

Osteoarthritis develops most commonly in the absence of a known cause (primary or idiopathic OA). Although OA usually affects all the tissues within the joint, the involvement of articular cartilage degeneration has been noticed in OA onset. The first stage of cartilage degeneration in OA involves PG loss, disruption of the collagen network, which is also visible as fraying or fibrillation in the cartilage surface, and increased water content (Buckwalter & Mankin 1998, Summers et al. 2008). During the second stage, chondrocytes are stimulated to synthesize matrix macromolecules, aiming at restoring the normal tissue structure and composition. This stage may last for years, and in some patients it may slow down or even reverse the degeneration, at least temporarily (Buckwalter & Mankin 1998). Extensive bone remodeling also takes place. The subchondral bone plate and calcified cartilage thickens, leading to a subchondral sclerosis, while the subchondral trabecular bone may even remain osteopenic because of the rapid turnover of bone in early OA (Burr & Gallant 2012). Later on, formation of cyst-like cavities might further accelerate cartilage degeneration in trabecular bone. Whether these subchondral bone changes occur at the same time as cartilage deteriorates, continues to be debated. Already decades ago, some studies (Radin et al. 1972, Radin & Rose 1986) suggested that stiffening of subchondral bone initiates progressive joint degeneration. Sclerotic subchondral bone is less able to attenuate and distribute forces through the joint, thus increasing the stresses in the cartilage and promoting cartilage degeneration (Radin et al. 1972, Radin & Rose 1986). Nevertheless, at the third stage, failure in chondrocyte activity leads to progressive loss of articular cartilage and increase in the cartilage stiffness. The matrix is further damaged, and without protection and stabilization of the matrix, death of chondrocytes will occur, signaling a "point of no return". Figure 4 shows the hypothesis of the etiopathogenesis of OA. At the end stage of OA, the articular cartilage is completely lost, leaving the thickened densed subchondral plate to function as the contact surface of the joint (Buckwalter & Mankin 1998).

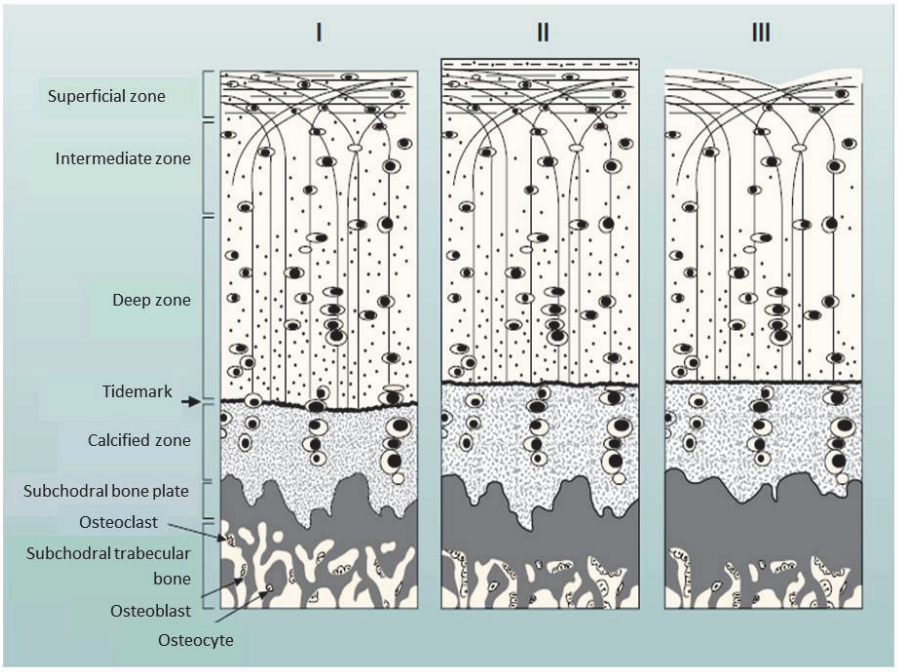


FIGURE 4 The Etiopathogenesis of osteoarthritis. Oval structures represent chondrocytes, dots represent glycosaminoglycans (GAGs) and curved lines represent collagen fibers. (I) Intact articular surface with high content of GAGs in uncalcified and calcified cartilage. (II) Depletion of GAGs in superficial and intermediate zones exposes the superficial collagen fibrils and leads either to disorganization or reorientation of the superficial zone collagen network, water influx and thickening and softening of cartilage. Simultaneously, calcified cartilage and subchondral bone plate grow thicker with increased remodeling of subchondral trabecular bone. (III) Additional loss of GAGs, fibrillation of cartilage surface and progression of subchondral bone sclerosis. Modified from Arokoski et al. (2000).

Typically, articular cartilage degeneration and subchondral plate thickening are accompanied by osteophyte formation. Osteophytes are found at the margin of cartilage and bone, and are considered stabilizing structures that redistribute biomechanical forces during loading. Osteophytes, however, limit natural motion of the joint and have been associated with pain and inflammation of the synovial membrane. The factors that determine osteophyte formation and growth are unknown. Synovial membrane inflammation has also been implicated in the pathogenesis of OA. Nevertheless, inflammation of the synovial membrane is less likely to be a primary cause of OA. Rather, synovitis is currently considered a secondary process induced by immune activation following cartilage damage (Sokolove & Lepus 2013).

Osteoarthritic changes in cartilage are sometimes erroneously considered to be a normal part of the aging process. However, the poor correlation of radiographic disease with symptoms and disability as well as the fact that many healthy older adults do not suffer from symptomatic OA indicate that aging and OA are not one and the same (Loeser 2007). Age related macroscopic cartilage changes, such as browning and some surface wear or roughening have been found in tissue donors who had no known prior history of OA (Cole et al. 2003). Whether these cartilage changes might represent early OA cannot be confirmed until longitudinal data is available on how these changes progress over time. Age-related decrease in cartilage hydration has also been found, which is reverse of the increase in hydration manifested in early OA (Grushko et al. 1989). At the microscopic level, the aging articular cartilage chondrocytes become less responsive to anabolic cytokines, presumably leading to reduced synthetic capacity and activity of chondrocytes, whereas osteoarthritic cartilage is associated with a prominent regenerative and reparative activity. Thus, aging articular cartilage does not cause OA: instead the age-related metabolic and phenotypic decline in the chondrocytes increases the risk for articular cartilage degeneration and limits the ability of the cells to repair the tissue once degenerative changes occur (Martin & Buckwalter 2002).

Risk factors and treatment

The best treatment for knee OA is prevention. Therefore the awareness of risk factors for the incidence of knee OA is of great importance at aiming at preventing the disease, especially among subjects who have several risk factors. Epidemiological studies and meta-analysis have showed that increased BMI, previous knee injury, low level physical activity, presence of Heberden's nodes and hand OA, female gender, older age, certain sporting activities (e.g., soccer, weight-lifting), certain physical occupational activities (e.g., kneeling, squatting) and increased bone mineral density (BMD) are risk factors for the onset of knee OA, whereas smoking appears to have a moderate protective effect against the disease (Felson & Chaisson 1997, Blagojevic et al. 2010). Also, acute and chronic injurious compressive overloads can lead to cartilage degeneration. In vitro studies have shown that static compression within the physiologic range can reversibly inhibit the synthesis of critical components of the cartilage matrix (DiMicco et al. 2003). Modifiable risk-factors for the incidence and/or progression of knee OA include physical activity level, obesity, manual labor, and muscle dysfunction. Physical activity is likely to be one key element in altering other modifiable risk factors. With adequate activity, weight loss or weight maintenance can be achieved, as well as improvement in muscle function. On the other hand, absence of physical activity through immobilization has been shown to lead to the loss of cartilage PGs, which, in turn, compromises cartilage health, promoting OA (Säämänen et al. 1987). Obesity, in turn, has been traditionally thought to contribute to the development of OA by excessive joint loading. This may not be the whole truth, however, because obesity is also linked to OA in non-weight-bearing hand and

finger joints (Yusuf et al. 2010). Recent studies imply that adipocytokine leptin may be a possible link between obesity and OA. Leptin levels in synovial fluid have been noticed to be increased in obese patients (Vuolteenaho et al. 2014, Thijssen et al. 2015).

As OA is not yet a curable disease, treatment focuses primarily on relieving symptoms, preventing disease progress, and preserving or improving physical function. Treatment of knee OA is a combination of non-pharmacological conservative modalities, pharmacological and surgical modalities (Arokoski et al. 2014). The conservative modalities form the basis of any therapeutic program for knee OA. These modalities include patient education and counseling, weight reduction, therapeutic exercise, and different assistive devices for walking and daily living. Physiotherapy is regarded as an important component of knee OA conservative treatment, and several therapy modalities, such as manual, thermal, electromagnetic and acupuncture have been used for the alleviation of symptoms and maintaining or improving patients' functional capacity. Although several studies have demonstrated that these modalities may offer short-term benefits in terms of pain and physical function, the overall effects of these interventions have been found small to moderate at best (Rutjes et al. 2009, Jansen et al. 2011, Negm et al. 2013, Corbett et al. 2013). Occupational therapy also has a role in improving the patients' ability to perform the activities of daily living. Pharmaceutical treatment should be used in pain management and function improvement as an additive therapy along with conservative therapies, or when the patient is unable to undergo total joint arthroplasty after failure to respond to conservative treatment modalities. Surgical treatments include tibial and femoral osteotomies, and at the end-stage of knee OA, knee joint replacement (Arokoski et al. 2014). Arthroscopic procedures with lavage or debriment have historically been common treatment for knee OA. Currently, however, they are not recommended in persons with a primary diagnosis of symptomatic knee OA owing to the lack of reliable evidence (American Academy of Orthopaedic Surgeons Board of Directors 2013, Thorlund et al. 2015).

2.1.3 Assessment of bone and articular cartilage

Bone and articular cartilage characteristics can be assessed in several ways. The following section presents the basic principles, advantages and disadvantages of the techniques most commonly used to measure bone and cartilage. The description of the DXA method has been emphasized in this literature review, as it was used in the empirical part of this doctoral thesis for the purpose of screening the study participants for the presence of OP and for monitoring the effects of exercise on bones. As mentioned earlier, DXA is the most widely used bone densitometry technique, since the absorption of X-rays is very sensitive to the calcium content of tissue, of which bone is the most important source (Kanis et al. 2013). The principle of DXA is to send a sufficient amount of X-rays with high- and low-energy photons through the tissues and to detect the remaining amount of energy after passage. X-ray beam energy is reduced more or less

depending upon the thickness and density of the tissues through which they pass. From these measurements, the DXA calculates BMD. It also counts the scanned area and, by multiplying these two values, calculates bone mineral content (BMC, g) (Crabtree et al. 2007). DXA-measurements can be applied at the lumbar spine or femoral neck and at peripheral sites like the wrist and calcaneus.

In general, DXA measurements are precise (Sievänen et al. 1996) and safe, as DXA uses a relatively low dose of ionizing radiation. The limitation of the DXA-technique, however, is that from a three dimensional object DXA is only able to provide two-dimensional "areal" data, which lack physicality. Thus, BMD is not a measure of volumetric density (g/cm^3), since it provides no information about bone depth (Kanis et al. 2013). DXA also inherently assumes that the scanned body region comprises only bone and homogenous soft tissue, which, given the differences in individuals' anatomy and body composition, is obviously not the case (Bolotin & Sievänen 2001, Järvinen et al. 2015a). At the femoral neck, BMD can be altered by degenerative arthritis, degree of internal rotation and overlying soft tissues (Agarwal & Camacho 2006). In the lumbar spine, degenerative changes seen in OA, ankylosing spondylitis, and structural abnormalities, such as compression fractures and scoliosis, may artificially elevate BMD values. It should also bear in mind that although BMD measurement can predict fracture risk, it cannot identify individuals who will sustain a fracture (Marshall et al. 1996).

Based on DXA scans, proximal femur structural rigidity can be estimated with Hip Structural Analysis (HSA) and Advanced Hip Analysis (AHA) computer programs. The purposes of these software programs are to improve the predictive value of femoral neck bone mineral data for OP risk assessment. Several structural variables can be derived from DXA-measurements, such as cross-sectional area (CSA, [mm^2], a surrogate for compressive strength), cross-sectional moment of inertia (CSMI, [mm^4], a surrogate for bending strength), width (W, [mm], a surrogate for breaking resistance of bone) and section modulus (Z, [mm^3], a surrogate for bending strength) (Beck et al. 1990, Beck 2007). Obviously, the same limitation of planar scans, as with DXA-based densitometry scans, applies to HSA and AHA analyses.

The quantitative computed tomography (QCT) method assess volumetric BMD (vBMC, mg/cm^3), thereby eliminating uncertainty about the third dimension of bone. QCT can measure cortical and trabecular bone separately, which is an advantage, as trabecular vBMD is more sensitive to changes in BMD (Ward et al. 2007). The limitation of the measurement is the approximately 10 - 12 times greater ionizing radiation dose than in DXA, although radiation exposure is lower when measuring at peripheral skeletal sites (pQCT) than at axial skeletal sites (Ward et al. 2007). In addition to QCT and DXA, bone mineral density as well as bone macro- and microstructure can be assessed with quantitative ultrasound (QUS). Ultrasound of the calcaneus or radius, which provides an index of bone stiffness, has been used in the assessment of OP risk. Ultrasound devices are widely available, measurement is

easy to perform, and it does not involve exposure to ionizing radiation. However, there is no evidence of the diagnostic value of QUS at the present time, and therefore it should be used only as a screening test (Kohrt et al. 2004, Wang et al. 2014). Moreover, magnetic resonance imaging (MRI) techniques can be also used in assessing bone characteristics. This method is discussed later in more detail in the context of cartilage assessment.

The diagnosis of OA is based on clinical findings, symptoms and radiographic joint changes. Radiographic imaging does not, however, offer direct information about the status of the articular cartilage and other articular tissues. Currently, MRI has become a promising technique for quantitative evaluation of the whole joint, including cartilage, bone, meniscus and ligaments (Majumdar 2010). In general, MRI techniques can be divided into those for clinical and those for research purposes. In clinical practice, standard MRI techniques are used to evaluate cartilage morphology, primarily in the diagnosis of focal lesions. Quantitative MRI (qMRI) techniques can be used for measuring parameters of cartilage morphology, such as tissue volume, thickness and surface area. In research practice, qMRI techniques have been developed to be sensitive to the biochemical and structural changes in the extracellular cartilage matrix that precede visible changes in cartilage (Mosher 2007). Currently, a number of different pulse sequences for assessing biochemical and structural composition of cartilage are available, but for the evaluation of hyaline articular cartilage, a typical MR protocol will include T1- and T2-weighted images with fast spin-echo-based sequences (Saadat et al. 2010).

T1-weighted images are most often used with paramagnetic contrast agents to enhance signal intensity and contrast between tissues. Delayed gadolinium enhanced MRI of cartilage (dGEMRIC) (Burstein et al. 2001) utilizes the T1 relaxation time in the presence of the paramagnetic contrast agent, gadolinium, embedded in diethylene triaminopentaacetate acid ($Gd\text{-}DTPA^{2-}$). When $Gd\text{-}DTPA^{2-}$ diffuses into cartilage, it will distribute in a higher concentration in areas in which the GAG content is relatively low and will be excluded from regions that are rich in GAG. By determining the distribution of $Gd\text{-}DTPA^{2-}$ one can quantify the GAG concentration of the cartilage (Burstein & Gray 2003). The correspondence of dGEMRIC to histology has been previously reported (Bashir et al. 1999, Nieminen et al. 2002). In general, the dGEMRIC index is reported to decrease with lowered GAG content, and the method appears to be a feasible biomarker of early degenerative changes in cartilage quality (Dahlberg et al. 2012). However, gender or age does not seem to affect the dGEMRIC index (Dahlberg et al. 2012). The dGEMRIC index has been observed to correlate with the mechanical properties of cartilage (Kurkijärvi et al. 2004, Samosky et al. 2005). The dGEMRIC technique has been applied in various clinical human studies among both healthy subjects and subjects with different knee-related pathologies (Bashir et al. 1997, Tiderius et al. 2003, Tiderius et al. 2004, Roos & Dahlberg 2005, Van Ginckel et al. 2010, Crema et al. 2014). Despite the widespread use of the dGEMRIC technique, knowledge of its

reproducibility has been limited, setting the scene for a systematically designed study on the topic.

In T2-weighted images, a significant relation has been found between collagen content and T2 value (Fragonas et al. 1998), although T2 has also been associated with proteoglycan (Wayne et al. 2003) and water content of cartilage (Lusse et al. 2000). However, since collagen is the most abundant macromolecule in cartilage, it is believed that collagen, specifically its content, orientation, and structure, is the main determinant of T2 relaxation in cartilage (Burstein & Gray 2003). Focal defects and age-related changes in cartilage are associated with increased T2 values (Mosher et al. 2000, Mosher et al. 2004). Moreover, an increased T2 value is associated with the severity of radiographic knee OA (Dunn et al. 2004) and histological degeneration of cartilage (David-Vaudey et al. 2004). These findings imply that T2 mapping may be a good marker for OA in cartilage, although longitudinal data are needed to confirm the associations between progression of OA and changes in cartilage T2 values.

The advantages of MR imaging techniques are that they use no ionizing radiation and have the ability to image all of the tissues in multiple anatomical planes without moving the object. In addition, the most recent MRI applications enable the simultaneous investigation of articular cartilage and bone (Rautiainen et al. 2013). The disadvantages of quantitative MR imaging are that they require long scanning times, and research protocols needs high-field high-resolution devices, which are not easily accessible. Besides the above-mentioned X-ray and MRI methods, biochemical markers (Hunter et al. 2014) arthroscopy, and an indentation instrument under arthroscopic control (Lyyra et al. 1995, Vasara et al. 2005) are being used in the assessment of articular cartilage. However, these issues are not addressed in this review.

2.1.4 Bone and cartilage interaction

For decades, studies have indicated that persons with OA of the hip or knee are more likely to have higher bone mineral mass or density at the peripheral and axial skeleton than healthy subjects or subjects with OP (Foss & Byers 1972, Dequeker et al. 1975). This phenomenon, which is also known as the inverse relationship between OA and OP, is a consequence of increased bone remodeling in early OA, although the causes of increased bone remodeling per se are unknown (Burr & Gallant 2012). An increase in BMD of about 10% at different skeletal sites has been found in large epidemiological studies with generalized OA patients, even after correction for body weight (Dequeker 1997, Dequeker 1999). In the Framingham study, BMD of the femoral neck was found to be 5 - 9% higher in both sexes with knee OA severity of grades 1 - 3 according the radiological grading scale of K/L, but not in the patients with most progressed disease severity, K/L grade 4 (Hannan et al. 1993). This may be caused at least partly by disuse of the limb, which eventually leads to bone loss. Furthermore, the forearm BMD of the patients with knee OA in the Framingham study was not elevated compared to those without knee OA (Hannan et al. 1993).

Confounding variables, such as race, obesity and physical activity, have been thought to explain the mutually exclusive relationship between OA and OP. For example, overweight individuals and/or those subjected to excessive physical activity could have a higher risk for developing OA and for having an elevated level of bone mass (Roman-Blas et al. 2009). It has been also argued that the fact that the association between OA and high BMD has been gained mainly from cross-sectional studies, does not necessarily mean that the presence of OA will not lead to an increase in BMD or the incidence of osteoporotic fractures (Im & Kim 2014). While the majority of the studies suggest that subjects, at least those with large joint OA, have increased bone mineral mass (Sambrook & Naganathan 1997, Im & Kim 2014), this does not necessarily mean that OA subjects are at lower risk for fracture. For example, in a large epidemiological study among postmenopausal women with fragility fractures, the presence of hip OA was seen on X–rays (Nevitt et al. 1996). In fact, some studies have indicated that OA and OP are not mutually exclusive and that the prevalence of OP in the OA population is virtually identical to that seen in the "normal" population (McDonald Blumer 2005). As the association between OA and OP remains controversial, longitudinal follow-ups with large sample sizes need to be undertaken to clarify the associations of these diseases.

2.1.5 Mechanical adaptation and biomechanical properties

During daily activities, the skeleton has to be able to cope without structural failure or fracture. It has to be strong enough to withstand the demands of physical activity and external forces, adaptive enough to respond to changes in these demands, and lightweight enough to allow effective energy-saving locomotion (Heinonen 2001). To meet all of these demands, the mechanical competence of bone comprises both intrinsic material properties and structural (or geometric) properties. Stress and strain are related to material properties of bone. Stress is the resistance that develops in response to the application of forces (Bouxsein 2006). It is measured in units of Newtons per square meter (N/m^2) or Pascals (Pa). Any local deformation that results from the forces applied is called strain. When forces are applied to bone, the distribution of stresses and strain varies across the bone structures (Bouxsein 2006). Depending upon its orientation, stresses and strain can be compressive, tensile, shear (pushing one part of a bone in one direction, and another part of the bone in the opposite direction), bending, torsion or their combinations (Bouxsein 2006). Strain is calculated by dividing the change in bone dimension by the original bone dimension (for example, compression slightly shortens and widens the bone), and is expressed as a fraction or percentage (strain of 0.1% = 1000 microstrain [μE]) (Heinonen 2001). Frost (1997) suggested that when strain reaches a minimum magnitude, the modeling phase is switched on (Frost 1997). This strain is called the minimum effective strain of modeling and has been suggested to lie near 1000 μE (Frost 1997). If the strain stays below the minimum effective level (50 – 100 μE), no remodeling will take place. This disuse mode increases permanent bone loss and tends to cause osteopenia

(Frost 1997). There is also a microdamage threshold. When loads exceed this threshold, the damage cannot be repaired by BMUs, resulting in a stress fracture. The microdamage threshold seems to lie near 3000 μE. The threshold for bone fracture is around 25 000 μE (Frost 1997).

With regard to bone strain, skeletal adaptation to mechanical loading is mainly dependent on strain magnitude, as mentioned above (Carter 1984, Rubin & Lanyon 1985), and strain rate, i.e., fast loading rate (Turner et al. 1995, Turner 1998). In addition, unusual distributions of strain arising from atypical loading directions (Lanyon 1992, Frost 2003, Frost 2004, Guadalupe-Grau et al. 2009) and strain cycles, i.e., the number of load repetitions that change bone dimensions at a given magnitude, determine to some extent bone adaptation to mechanical loading. For example, Rubin & Lanyon (1984) suggested that only 36 consecutive loading cycles, repeated more than once a day, would be enough to improve bone strength (Rubin & Lanyon 1984). In their same animal experiment they also noticed that dynamic loading is much more efficient for strengthening bone than static loading (Rubin & Lanyon 1984). This is in line with the findings of Nikander et al. (2005) where a high-magnitude type of loading (weightlifting) was not associated with an increase in femoral neck bending strength in these athletes when compared with athletes representing high-impact (volleyball, hurdling) or odd-impact loading modalities (squash, soccer, speed-skating, step-aerobics) (Nikander et al. 2005). Moreover, all bone responses to mechanical strain are site-specific. While one region of the skeleton may experience a net loss of bone, another region may at the same time experience a net gain (Carter 1984, Heinonen 2001).

The structural properties of bone include size, shape, cortical thickness, cross sectional area, and trabecular architecture (Heinonen 2001). As mentioned earlier, during growth the skeleton adapts to loading by modeling. However, in adults modeling becomes ineffective in cortical bone, but in trabeculae it can continue throughout the life-span (Frost 1992). In addition, in adults appendicular bone adapts to mechanical loads by endosteal resorption and periosteal apposition of bone tissue. This increases bone diameter and thus provides greater resistance to loading (Frost 1992, Heinonen 2001). According to the classical Wolff's Law (1892), form follows function (Frost 1994). However, currently there is also some evidence that increased mechanical loading may induce a redistribution of bone minerals from the trabecular to cortical component without any external bone expansion (Heinonen et al. 2001a, Heinonen et al. 2012).

For articular cartilage well-being, physical/mechanical forces are crucial across the whole life-span. During embryonic development, skeletal muscle contractions are essential for the diarthrodial joints, and lack of muscular movements inhibits formation of normal joint structures, such as articular cartilages and joint cavities (Persson 1983). In children, physical activity has been shown to be associated with knee cartilage development, in much the same way as bones (Heinonen et al. 2001b), in both cross-sectional and longitudinal studies, suggesting that in children articular cartilage adapts as a

consequence of increased loading (Jones et al. 2000, Jones et al. 2003). In adulthood, mechanical loading is needed to maintain the normal state and functions of articular cartilage and subchondral bone (Arokoski et al. 2000). In contrast, there is good evidence that under reduced loading conditions, such as postoperative immobilization and paraplegia, cartilage undergoes atrophy (Vanwanseele et al. 2002, Vanwanseele et al. 2003, Eckstein et al. 2006a). The mechanism underlying the potential of cartilage for increased loading adaptation is considered to include both structural and functional properties. Regular mechanical loading of cartilage and chondrocytes leads to an intracellular signaling cascade, which results in higher PG and GAG content (Slowman & Brandt 1986, Kiviranta et al. 1987, Tiderius et al. 2004), higher cell volume (Eggli et al. 1988) and bigger compressive stiffness (Swann & Seedhom 1993) compared to cartilage which is not subjected to a high level of stress. Increased joint loading in athletes is associated with an increase in the load-bearing area, rather than an increase in cartilage thickness, to reduce the effects of high stress on cartilage (Eckstein et al. 2002). Thus, mechanical loading maintains healthy cartilage by regulating tissue remodeling.

When an external load is applied to a joint, the cartilage deforms to increase the contact area and decrease contact stress. Loading and deformation of cartilage generate a combination of tensile, compressive and shear stresses in the cartilage (Setton et al. 1999). During tension, when the tensile stress is relatively small, a "toe-region" is seen in the stress-strain curve primarily due to the realignment of the collagen network. With greater tensile force, the collagen fibers themselves are stretched (Woo et al. 1976, Roth & Mow 1980). The proportionality constant in the "linear" region of the tensile stress-strain curve is known as "Young's modulus" or the "Tensile modulus". The tensile modulus is a measure of resistance to tensile loading, and depends on the density and orientation of collagen fibers, fiber diameter, type or amount of collagen cross-linking, and the strength of the ionic bonds and frictional interactions between the collagen network and the PG network (Akizuki et al. 1986, Mow et al. 1992, Guilak et al. 1994, Mow & Hung 2003). Figure 5 shows a typical stress-strain curve for articular cartilage in an uniaxial experiment. In general, the tensile modulus of healthy human articular cartilage varies within the range 5 - 25 MPa, whereas in OA subjects the tensile modulus has been shown to be up to 90% lower (Akizuki et al. 1986), testifying to the role of collagen in the regulation of stiffness properties. In compression, hydraulic permeability depends primarily on PGs (Mow et al. 1984).

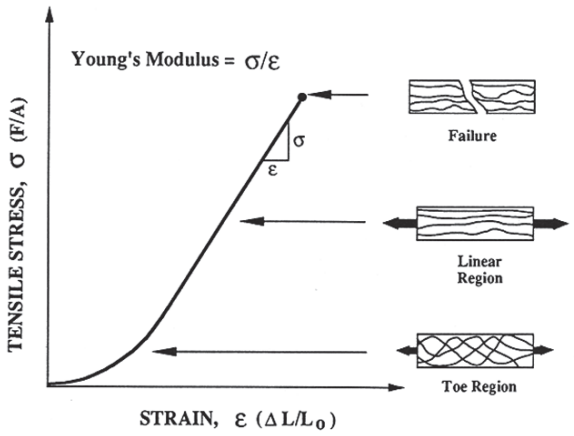


FIGURE 5 Characteristic stress-strain relationship for articular cartilage in a steady strain-rate tensile experiment. As the cartilage is pulled in tension, the stress increases non-linearly in the toe region as randomly oriented collagen fibrils align themselves in the direction of loading. In the linear region, the tensile stress increases linearly as the collagen fibrils are stretched until fracture occurs. A and L_0 are the initial cross-sectional area and length of the specimen, respectively. F and ΔL are the tensile force and change in length, and ε and σ are the tensile strain and stress, respectively. Figure freely accessible on the internet. Text adapted from Mow & Hung (2003).

From a clinical point of view, different joint loads and stresses are transmitted to the articular cartilage during locomotion depending upon the type of physical activity and joint structure. For example, knee implant compressive forces ranging from 2.2 to 3.5 times the subject's body weight (BW) have been measured for activities of daily living (Kutzner et al. 2010) while a peak tibiofemoral compressive force of 10.4 BW has been reported during running (Messier et al. 2008). An example of extreme impact loading on the knee joint is triple jump training, where maximum forces over 15 times BW has been measured from ground reaction forces (Perttunen et al. 2000). Obviously, this magnitude of joint loading is excessive when compared to the average load on the knee in everyday activities, but it shows that at its best cartilage is able to withstand high forces associated with weight-bearing and joint motion over decades without damage. Seen in this light, the elastic modulus of cartilage (designating the "stiffness" of tissue) estimated to be around 0.5-1.0 MPa (500 000-1 000 000 Pa) (Mow et al. 1984, Jurvelin et al. 1987) appears to be rather low. However, due to the relatively small permeability of the cartilage, the interstitial water cannot escape from tissue during dynamic loading but is pressurized, thereby giving support against loading. This explains why, cartilage stiffness can be 10 times higher during dynamic loading than the intrinsic modulus of the matrix (Jurvelin et al. 1990, Jurvelin et al. 1997). Moreover, menisci are important weight-bearing structures on the tibial plateaus and may carry over half of the exposed knee joint load (McBride & Reid 1988). In addition, viscoelastic properties of the knee and muscle

contraction modify and absorb the impact loading applied to the knee joint when walking, running and jumping. When muscles are acting as a shock absorber, biomechanical in vitro studies have demonstrated that articular cartilage accounts for only 1 - 3% of the total force attenuation in the joint, while the joint capsule, subchondral bone and cortical bone each account for over 30% of the impact attenuation (Radin et al. 1970, Hoshino & Wallace 1987). If subchondral bone becomes sclerotic, however, it is less able to absorb and dissipate the impact energy, which in turn increases the force transmitted through the joint (Hoshino & Wallace 1987). Thus an osteoarthritic knee joint with articular cartilage failure and/or sclerotic subchondral bone will absorb only about half as much load as the normal knee (Hoshino & Wallace 1987).

2.1.6 Other factors influencing bone and cartilage properties

In addition to mechanical loading, many other factors affect bone and cartilage properties. It is important to be aware of these factors, since with, for example, bones environmental factors account for only about 10% at the population level, whereas age and genetic factors have the greatest influence on bone mineral content (Khan et al. 2001b). In addition to age and genetics, this chapter also explores some other factors of importance to bone and cartilage health, especially in postmenopausal and elderly women, who form population most susceptible to OP and OA.

Age and bone

The peak bone mass is most often reached during young adulthood around the age of 20 (Matkovic et al. 1994, Haapasalo et al. 1996). High peak bone mass is important for protection against fragility fractures later in life. With increasing age, bone loss accelerates. At some stage of adulthood, remodeling increases, the BMU balance deteriorates a lower volume of bone formation than of bone resorption, and periosteal apposition declines. All these accelerate cortical bone thinning and increase porosity, as well as trabecular bone thinning and loss of connectivity. Bone stiffness declines owing to its predisposition to microdamage due to the replacement of older densely mineralized bone with younger less densely mineralized bone (Seeman 2008). The most rapid bone loss takes place during the late perimenopause and in the first postmenopausal years, lasting altogether for 4 – 8 years (Finkelstein et al. 2008). During that time, the annual bone loss may be 1 - 2% depending upon the site measured. The rate of loss appears greater at the trabecular vertebral bone than at the more cortical femoral or radial sites. Bone loss slows in the 3 - 5 years post menopause as the loss steady state is restored at a new higher remodeling rate by the large number of BMUs created in the perimenopause (Seeman 2008). To summarize, about 10% of bone is lost per decade until around age 75, when it levels off to about 3% per decade (Khan et al. 2001c).

Age and cartilage

The prevalence of multifactorial forms of OA increases rapidly with age, beginning in women at about the age of 40 - 50 years (Nevitt & Felson 1996). By the age of 60, almost 80% of the population will have radiographic evidence of OA in at least one joint (Lawrence et al. 1966). Since OA is common in the older population, it is sometimes considered to be a normal part of the aging process. However, the poor correlation between radiographic OA and symptoms or disability, together with the fact that many healthy older adults do not suffer from symptomatic OA indicate that aging and OA are not one and the same thing (Loeser 2007).

As previously described in the context of structure and function of the articular cartilage, several age-related changes take place in cartilage, such as some surface wear and thinning, browning, calcification and sometimes ossification (Loeser 2007). Whether these changes also represent early OA cannot be confirmed until longitudinal data is available on how these changes progress over time. However, some of the articular cartilage changes that occur with aging differ from those that may be related to the development of OA. For instance, whereas aging induces decreased cartilage hydration, early OA shows increased hydration (Grushko et al. 1989). Moreover, in aging cartilage there is no change in total collagen and PG content whilst osteoarthritic cartilage is characterized by a progressive loss of collagen and PG (Grushko et al. 1989). Similarly, there is little to no proliferation in chondrocyte function with aging, while increased proliferation and clustering have been observed in OA when the matrix is damaged (Loeser 2007). This is thought to represent an attempt to repair the damaged matrix by increasing the number of cells.

Genetics and bone

Twin and family studies have shown that genetic factors account between 50 and 85% of an individual's bone mass or density (Smith et al. 1973, Krall & Dawson-Hughes 1993, Gueguen et al. 1995, Slemenda et al. 1996). However, the effect of heredity seems to vary between skeletal sites (Havill et al. 2007, Mikkola et al. 2008), and age and phase of life, depending also upon hormonal factors, diet and lifestyle habits (Eisman 1999). A clinically important question is whether genes determine osteoporotic fractures, as it is well recognized that family history is a strong predictor of risk for osteoporotic fractures (Cummings et al. 1995, Torgerson et al. 1996). Fracture, however, is complex phenotype, since many other factors, such as falls, independently of BMD, increase the risk of likelihood of fractures. For example, an increased risk of falling with aging, some biochemical markers of bone turnover, and various aspects of femoral neck geometry in different ethnic groups render genetic analysis of fracture risk a highly challenging task (Ralston & Uitterlinden 2010). Unsurprisingly, conflicting results have been reported on the heritability of fracture. While some studies have not provided strong evidence to suggest that fractures are heritable (Kannus et al. 1999); for example, heritability estimates for in wrist fracture in postmenopausal women have varied between 25% (Deng et al. 2000)

and 54% (Andrew et al. 2005). Overall, the heritable component of osteoporotic fractures is considered to lessen with age, as environmental factors, such as risk for falls come into play (Ralston & Uitterlinden 2010).

Genetics and cartilage

With regard to cartilage properties, most heritability studies have focused on the genetic contribution via epidemiological and twin OA studies. These studies have shown that OA has a strong genetic influence, with an estimated contribution to the risk for radiographic hand or knee OA in the range 39 - 65% (Spector et al. 1996, Felson et al. 1998). A more recent study by Riyazi et al. (2005) has, however, shown that the genetic contribution to knee OA in sibling pairs may be much less than at other sites, such as the hips, hands and spine (Riyazi et al. 2005). There are also some findings showing that the genes which are involved in OA are associated with bone density, and with inflammation and degradation of cartilage (Nakajima et al. 2010), although not all findings on the topic concur (Shi et al. 2010). These aforementioned, somewhat divergent, results point to the complexity of the role of the genetic component in knee OA. While OA is a polygenic disease, all the genes and allelic variants which predispose to OA are difficult to identify accurately due both to the complexity of the disease, which is a blend of symptoms and signs with multiple causes, and to the genetic diversity of different populations (Näkki 2012).

Hormonal regulation and bone

The onset of menopause and the loss of ovarian function are associated with a significant increase in the prevalence of both OA and OP (Stevenson 2011). Sex hormone alterations, primarily estrogen deficiency due the loss of ovarian function, has been suggested as the possible initiator of the development of these diseases (Roman-Blas et al. 2009, Khosla 2010). It has been reported that estrogen has direct effects on collagen, cytokines and matrix metalloproteinases (enzymes degrading proteoglycan), and that at certain doses estrogen may be beneficial by improving bone and articular tissue remodeling (Wluka et al. 2000). In fact, a number of hormone replacement therapy (HRT, i.e., estrogen given with progesterone) studies have shown a positive protective effect on bone density and osteoporotic fractures in postmenopausal women (Nelson et al. 2002, Wells et al. 2002, Mikkola et al. 2011). However, reports of increased risks of coronary heart disease, stroke and breast cancer had reduced the use of HRT in the treatment of OP by the end of 1990, since when the decision whether or not to take HRT to decrease OP has been based on a more accurate individualized risk-benefit analysis (Shoupe 2011, Rozenberg et al. 2013). In addition to estrogen, many other hormones, such as parathyroid hormone (PTH), vitamin D, growth hormone, steroids and calcitonin are important regulators in bone metabolism (Guyton & Hall 2006).

Hormonal regulation and cartilage

In relation to OA, failure of estrogen production at menopause is strongly associated with hot flushes, the most common menopausal symptom

(Oldenhave et al. 1993), and with a relevant loss of muscle mass and, therefore significant impairment of muscle performance and functional capacity (Sipilä 2003). Whereas previously it was thought that joint structures and cartilage tissue were non-responsive to estrogen and estrogen deficiency, considerable efforts have been made recently to understand the potential role of estrogens in OA development and progression (Roman-Blas et al. 2009). In the observational clinical studies where the effects of estrogen replacement therapy (ERT) on OA has been studied in postmenopausal and elderly women, mixed (Roman-Blas et al. 2009) or limited evidence (de Klerk et al. 2009) on the effectiveness of ERT in preserving and restoring joint tissue has been reported. Due to limited understanding of the different molecular mechanisms by which estrogen deficit acts on articular tissues and their contribution to OA development, more basic research is called for to provide knowledge that can be translated this into real world effectiveness.

Nutrition and bone

Various different nutrients, such as calcium, vitamin D, phosphorous, magnesium and proteins are widely known to be required for bone growth, development and maintenance, but there are also many others. In OP and fracture prevention, two of the most well-known and well-studied nutrients are calcium and vitamin D (Christianson & Shen 2013). Calcium is particularly important for bone development. If calcium intake is insufficient when bones are growing and developing, they may never reach full strength or peak bone mass. In Finland, the recommended daily intake of calcium is 800 mg for women of all ages (Valtion ravitsemusneuvottelukunta 2014), while in the USA the corresponding values are 1000 mg for women aged 50 years or younger, and 1200 mg for women aged 51 or older (Ross et al. 2011). Food is the best source of calcium, and there are several calcium-rich food sources, such as dairy products and certain green vegetables. Although dietary sources of high-calcium foods are currently rather well-known, it may nevertheless be challenging for women to meet recommended calcium intake requirements. For example, a National Health and Nutrition Survey performed in 1999 and 2000 in the United States showed that calcium intake in women was below the lower reference nutrient intake: an average of 744 mg daily for ages 40 to 59, and an average of 660 mg daily for women over 60 years of age (Ervin et al. 2004). In the systematic review by Uusi-Rasi et al. (2013) high calcium intake (~800 – 1000 mg/day) had a small positive effect on bone mineral mass or density in postmenopausal women (Uusi-Rasi et al. 2013). However, the authors found the evidence that calcium supplementation reduces fracture incidence both scarce and inconsistent (Uusi-Rasi et al. 2013). Correspondingly, Bolland et al. found in their recent systematic review (2015) that calcium intake was not associated with risk for fracture, and that increasing calcium intake did not prevent fractures (Bolland et al. 2015).

Vitamin D is essential for intestinal absorption of calcium and its physiological regulation (Christianson & Shen 2013). In addition to its

importance for bones, vitamin D is also has a direct effect on articular cartilage by stimulating the synthesis of proteoglycans (Gerstenfeld et al. 1990). Most vitamin D can be produced subcutaneously from the action of sunlight, but it is also found in oily fish, fish oils, meat (particularly liver), eggs and dairy products. In addition, vitamin D supplements are recommended for those who do not get enough vitamin D from sunlight or food. For instance, a few studies in Nordic populations have shown that vitamin D serum concentrations in 50 - 90% of the study populations were insufficient during wintertime (Andersen et al. 2005, Thuesen et al. 2012). The current recommended vitamin D daily intake in the Nordic countries is 10 µg for both women and men less than 75 years of age, and 20 µg in women and men over 75 years of age (Nordic Council of Ministers 2014). In the USA the corresponding recommended values, assuming minimal sun exposure, are 600 international unit (IU) (equals 15 µg) for children and most adults, and 800 IU (equals 20 µg) over age 70 (United States Department of Agriculture). Vitamin D deficiency may lead to rickets in children and to osteomalacia (softening of bones) in adults. Use of vitamin D plus calcium is very common in postmenopausal women. The efficacy of vitamin D with or without calcium supplementation among older postmenopausal women preventing fractures, however, is uncertain and may vary from group to group and baseline vitamin D status (Chung et al. 2011, Aggarwal & Nityanand 2013).

Nutrition and cartilage

Previous *in vitro* studies have shown that omega-3 polyunsaturated fatty acids (PUFA), as found in oily fish and fish oils have anti-inflammatory aspects on cartilage metabolism (Curtis et al. 2002a, Curtis et al. 2002b). Evidence of their efficacy in the alleviation of the symptoms in rheumatoid arthritis is relatively strong (Wang et al. 2004, Calder 2006). However, for OA there is a relative paucity of well-designed large controlled trials on the topic, and therefore the benefit for pain alleviation has not been proven. Instead, a few studies indicate that fish oil taken as an adjunct to ibuprofen (Stammers et al. 1989) or to glucosamine sulfate (Gruenwald et al. 2009) might be beneficial in pain alleviation.

Previous studies have argued that glucosamine as such, and chondroitin sulfate are effective in improving symptoms and in having structure-modifying effects (Wang et al. 2004). The combination of glucosamine and chondroitin sulfate was also shown to be more effective than either alone (Clegg et al. 2006). However, recent meta-analyses have reported that the efficacy of glucosamine (Towheed et al. 2005, Wandel et al. 2010) or chondroitin (Wandel et al. 2010) in the treatment of hip or knee OA is no different from that of placebo treatment. Therefore, these compounds are not currently recommended in the treatment of knee OA by the Finnish Current Care Guidelines. Further, many studies have been conducted on the effects of antioxidant vitamins, such as vitamins C, E, beta-carotene and selenium (Wang et al. 2004, Canter et al. 2007) and non-antioxidant vitamins, such as vitamins D and B in the treatment of OA (Wang et

al. 2004, Calder 2006, Zhang et al. 2014). A recent longitudinal study reported that vitamin D deficiency predicted the progression of knee OA (Zhang et al. 2014). However, a prior RCT on vitamin D supplementation over 2 years did not find that it influenced knee pain or cartilage volume loss over placebo (McAlindon et al. 2013). Thus, it seems implausible that non-antioxidant vitamin D is capable of structural cartilage protection.

2.2 Physical activity and exercise in improving bone and cartilage health

2.2.1 Effects of physical activity on bones and cartilages

Physical activity plays an important role in the maintenance of bone mass (Sinaki 1996). Several studies show a positive relationship between habitual physical activity and BMD in postmenopausal women (Uusi-Rasi et al. 1998, Damilakis et al. 1999, Kaptoge et al. 2003, Devine et al. 2004). Moreover, physical activity has been associated with geometric indices of bone strength in the proximal femur in postmenopausal women (Nurzenski et al. 2007). In studies where the intensity of physical activity has been measured as acceleration levels, physical activity including acceleration levels of 3.9 g (=gravity) or more has been positively associated with femoral neck BMD changes in healthy premenopausal women (Vainionpää et al. 2006).

As well as being essential for bone integrity, physical activity is also vitally important for cartilage health, and should therefore always be incorporated into any therapeutical approach (Roddy et al. 2005). Increased physical activity has many beneficial effects on OA patients' health, such as weight reduction, improved aerobic capacity, and improved postural stability and muscle strength. Increased physical activity is also related to higher knee cartilage GAG content as investigated by dGEMRIC (Tiderius et al. 2004). Of these, muscle strength is of particular importance, since reduced muscle strength is a risk factor for knee OA development in women (Slemenda et al. 1998, Segal et al. 2010). Quadriceps weakness, in particular, has been thought to contribute to the onset and progression of knee OA (Glass et al. 2013). The mechanism whereby reduced muscle strength could be related to OA development is not unequivocal, but it has been suggested that muscle weakness could cause a shift in the mechanical axis, moving the joint load to areas not capable of coping with increased compression, and so causing local over-load (Andriacchi et al. 2004). In addition, muscle function is important in providing anteroposterior stability to the knee due to ligamentous laxity (Johansson et al. 1991) and in shock-absorbing by reducing the impact loading of the knee joint during ambulation (Jefferson et al. 1990). In this context, the muscles act as large rubber bands by doing "negative work" and by preparing the neuromuscular units to absorb an impact load by reflexes requiring approximately 75 ms (Brandt et al. 2006).

Even the small unexpected loads are considered to be much more damaging to the joints than large loads that have been anticipated (Brandt et al. 2006). Failure in neuromuscular function related to OA is called "muscle dysfunction", and currently the evidence supports the muscle dysfunction hypothesis as a cause of exercise-related OA over the "wear and tear" hypothesis, that is, gradual thinning of the articular cartilage due to repeated weight bearing activity of the joint (Shrier 2004). According to Shrier, this, manifested as physical activity and moderate intensity impact sports, rather reduces than worsens the symptoms of OA (Shrier 2004).

2.2.2 Exercise in maximizing bone strength

As mentioned, bone adaptation to increased loading is mainly dependent on the strain magnitude within the bone tissue and the rate at which the strain occurs (Rubin & Lanyon 1985, Turner et al. 1995). Direct quantification of strain magnitude in studies of exercise intensity is rarely possible, which is why different estimates such as an osteogenic index, (i.e., the product of strain magnitude and rate) (Turner & Robling 2003) and less direct methods, such as a given percentage of maximal heart rate or of one repetition maximum have been used to evaluate the bone loading forces of a given exercise. To date, more surrogate measures have become available to evaluate the magnitude of strain. These techniques include strain gauge measurements from the bone surface, ground reaction force (GRF) measurements, computational methods and accelerometer measurements (Ahola 2010). An accelerometer–based bone exercise recorder is advantageous since it can show not only the intensity of the steps in terms of acceleration magnitude value but also the number of steps (Ahola 2010). It has been shown that the acceleration signal measured from the hip highly resembled the GRF signal (Servais et al. 1984), and accelerometers are currently a widely accepted and used method of assessing human motion in clinical setting and everyday life (Mathie et al. 2004).

By using an accelerometer–based bone exercise recorder, the causal relationships between high-impact loading activity and proximal femur strength improvement have been studied in RCTs with Finnish and Japanese healthy premenopausal women (Vainionpää et al. 2006, Niu et al. 2010). In the Finnish study by Vainionpää et al. (2006), the number and intensity of acceleration peaks (impacts) at different acceleration levels revealed that impacts exceeding forces of 3.9 g were associated with positive response in women's femoral neck BMD. Less than 100 accelerations per day at 3.9 g were needed to improve hip BMD over the threshold level (Vainionpää et al. 2006). In turn, a higher acceleration level (> 5.4 g) was needed to induce an osteogenic effect at lumbar spine level L1 whereas a lower acceleration level of 1.1 – 2.4 g was sufficient in the calcaneus (Vainionpää et al. 2006). An acceleration level exceeding 4 g was also found pivotal in the cross-sectional study by Deere and colleagues (2012), in which adolescents' habitual level of high-impact activity was positively associated with femoral neck BMD and geometry (Deere et al. 2012). An acceleration level of 4 g represents an impact of four times body

weight and corresponds to impacts that can occur during jumping exercises or running at a speed of at least 10 km/h (Sievänen 2012).

In addition to the magnitude and rate of the influence of strain on bones, another clinically important factor in maximizing the osteogenic effect of exercise is the recovery time allowed between sessions. Using the isolated avian ulna model, Rubin and Lanyon (1984) showed that dividing the daily loading into two sessions instead of single training session can even double the improvement in bone strength (Rubin & Lanyon 1984). Moreover, Umemura et al. (2002) demonstrated in rats that a longer (30-sec) interval between individual loadings was more effective than a short (3-sec) interval (Umemura et al. 2002). Presumably, the rest period between loading sessions is needed to modulate the osteogenic response (Rubin & Lanyon 1984, Umemura et al. 2002, Turner & Robling 2003). In their quest to determine the optimal number of training sessions per week, Fuchs and co-workers conducted an experiment to study the effects of high-intensity jumping on hip and lumbar spine bone mass in children (Fuchs et al. 2001). Jump training improved BMC when performed 3 times per week, but when the number of sessions was reduced to 2 times per week, jumping had no significant effect on bone mass (Fuchs et al. 2001). Thus, strain magnitude, number of loads, time between sessions, and dynamic variable loadings are the primary mechanical factors in maximizing the osteogenic effects of exercise (Turner & Robling 2003). Nonetheless, all bone loading is probably beneficial for bones, but when an osteogenic bone response is desired, the above-mentioned factors should be taken into account when planning and executing individualized exercise regimens.

2.2.3 Exercise in preventing osteoporosis, falls and fractures

Current generally accepted strategies to improve bone strength and reduce the incidence of osteoporosis are to maximise peak bone mass during growth (childhood and adolescent), minimise age-related bone loss (middle-aged adults/premenopausal women), and prevent falls and fractures (in older adults/postmenopausal women) (Kohrt et al. 2004). During childhood and adolescence, bone mass is higher in children who are physically active than in less active children (Slemenda et al. 1991), and higher in children who participate in activities generating high-impact forces than in children who are involved in activities generating lower impact forces, such as swimming (Cassell et al. 1996, Courteix et al. 1998). Based on the theory that high-impact forces produce greater bone mineral acquisition than low-impact forces, several intervention trials have been implemented as part of school programs (Morris et al. 1997, Heinonen et al. 2000, Fuchs et al. 2001, Petit et al. 2002, MacKelvie et al. 2003, MacKelvie et al. 2004). These studies have consistently shown that children and adolescents who take part in jumping and calisthenics programs increase their bone mass or structure more than counterparts who take part in the usual activities. Obviously, the results of these experimental studies do not guarantee life-long bone mass maintenance, but they suggest that physical

activity including high-impact loading could provide protection against risk for OP in later life.

During the premenopausal years alone, 15% to 25% of BMD may be lost if prevention of bone loss is not properly addressed (Dolan et al. 2006). High-impact exercise interventions have yielded promising results in enhancing bone health in premenopausal women (Bassey & Ramsdale 1994, Heinonen et al. 1996, Bassey et al. 1998, Bailey & Brooke-Wavell 2010). Animal experiments showing that even brief exposure to strain is sufficient to produce an osteogenic effect (Rubin & Lanyon 1984, Rubin & Lanyon 1985, Umemura et al. 1997) have prompted increasing interest in the effects of brief lifestyle exposures to bouts of high-impact exercise on bone health. This approach favors premenopausal women, who may not have the opportunities to engage in regular exercise (Clark 2003). For example, in their meta-analysis, Babatunde at al. (2012) found a positive effect of brief, high-impact exercise on bone mineral mass among healthy premenopausal women. The results from six RCTs showed that brief exercise sessions (<30 min) improved BMD at the hip but not at the lumbar spine. These findings suggest that brief high-impact exercise, which is feasible enough to be incorporated into daily life may have a role in reducing hip fragility (Babatunde et al. 2012).

In postmenopausal women, weight-bearing exercise has been recommended for prevention and management of OP. The current guidelines are, however, equivocal regarding what kind of weight-bearing exercise would be the most effective for optimum bone mass maintenance. Over the years a number of RCTs and meta-analyses have been conducted in postmenopausal women to assess the effects of different exercise programmes on bone mineral mass (Kelley 1998a, Kelley 1998b, Kelley 1998c, Wolff et al. 1999, Kelley et al. 2002, Bonaiuti et al. 2002, Martyn-St James & Carroll 2006, Martyn-St James & Carroll 2008, Martyn-St James & Carroll 2009, Howe et al. 2011, Marques et al. 2012, Kelley et al. 2012, Ma et al. 2013) and structure/strength (Hamilton et al. 2010, Nikander et al. 2010, Polidoulis et al. 2012). Most of the meta-analyses and RCTs have shown a modest effect of exercise in maintaining bone mineral mass at the most common sites of OP-related fractures in the hip or spine (Kelley 1998b, Kelley 1998c, Wolff et al. 1999, Kelley et al. 2002, Bonaiuti et al. 2002, Martyn-St James & Carroll 2008, Howe et al. 2011, Marques et al. 2012, Kelley et al. 2012). In the meta-analyses by Martyn-St James & Carroll (2009), which focused, in particular, on the effects of differing impact training protocols on BMD in the hip and spine of postmenopausal women, the exercise protocols of the 15 included studies were categorized according to the impact classifications described by Nikander et al. (2005). Based on this classification, two trials evaluated the exercise protocols of high-impact loading (such as vertical jumping or skipping), five trials evaluated the exercise protocols of odd-impact loading (such as aerobic or step classes), four trials evaluated combined loading protocols (such as high-impact exercises with resistance training) and four trials evaluated the effects of low-impact protocols (such as walking, jogging or stair climbing). The high-impact exercise or odd-impact exercise protocols showed

no positive effects on BMD either at the femoral neck or lumbar spine. However, the combined loading and low-impact protocols had positive effects on both hip and spine BMD. The largest effect sizes were observed from protocols that combined jogging with walking and stair climbing. The authors suggested that these specific exercise modalities provide adequate loading stimulus for BMD increase in postmenopausal women, and that it is not reasonable to recommend exercise programs which are based on only the impact components alone (Martyn-St James & Carroll 2009).

Fall and fracture prevention

Although low hip bone density is strong predictor of hip fracture on the population level (Cummings et al. 1993), other physical performance-related risk factors for falls and fractures exist, such as muscle weakness, balance and gait deficit (Karinkanta et al. 2010). Therefore, multicomponent exercises, including elements of balance and strength training, as well as osteogenic exercises, aimed at increasing bone strength, are important for the prevention of falls and fractures in older adults. In a meta-analysis (2013) of 17 trials and 4 305 participants, multicomponent exercise programs significantly reduced the rate of injurious falls in community dwelling older adults (El-Khoury et al. 2013). The estimated reduction was 37% for all injurious falls and 61% for falls resulting in fractures. Most of the exercise trials embedded in the review by El-Khoury et al. were multicomponent programs including elements of balance training, gait, functional training, strengthening exercises, flexibility and endurance. However, exercise programs, particularly those emphasizing combined balance and strength training, have been shown to be an effective method of preventing falls (Karinkanta et al. 2010, Gillespie et al. 2012, Uusi-Rasi et al. 2015, El-Khoury et al. 2015).

As with fall prevention, some randomized trials have found that treating low BMD in elderly women also reduces the number of fractures (Korpelainen et al. 2006, Karinkanta et al. 2007) and that exercise reduces injurious falls and fractures in older women even after a 5-year follow-up period (Karinkanta et al. 2015). Also, somewhat surprisingly, even walking is associated with lower risk for hip fracture in postmenopausal women. This was found in a prospective cohort study, where walking for at least 4 h/week was associated with a 41% lower risk of hip fracture compared with walking for less than 1 h/wk (Feskanich et al. 2002). This is an encouraging finding, as walking per se may increase femoral bone density (Kohrt et al. 1997). Moreover, walking is also relatively safe as well as the most common physical activity among older adults.

2.2.4 Exercise in the treatment of knee osteoarthritis

Current international guidelines recommend exercise therapy as a first-line conservative management strategy for OA (Hochberg et al. 2012, McAlindon et al. 2014). These recommendations are largely based on the results from RCTs and systematic reviews (Bartels et al. 2007, Fransen & McConnell 2008, Fransen et al. 2010, Jansen et al. 2011) showing that exercise significantly reduces pain

and improves function. In the RCTs that have most often been targeted at subjects with mild to moderate knee OA, the exercise interventions applied have varied considerably in content and dosage. The vast majority of exercise studies have not attempted to evaluate the influence of exercise dosage (e.g., frequency, intensity, and duration) on treatment outcome; instead the main focus has been on finding optimal types of exercise for subjects with OA. Several types have been proposed in the literature that may be suitable for people with OA. These exercise studies include muscle strengthening exercises, aerobic exercises, aquatic training, balance retraining, proprioceptive retraining, functional exercise programs, neuromuscular retraining and coordination, and mixed /combination programs (Bennell et al. 2011). Of these exercise modalities, clinical trials have provided the strongest evidence for the efficacy of muscle conditioning and aerobic exercise in reducing pain and patient-reported disability in knee OA (Minor et al. 1989, Ettinger et al. 1997, van Baar et al. 1999, Baker & McAlindon 2000, Lin et al. 2009, Juhl et al. 2014).

Muscle strengthening exercises

Muscle strengthening exercise or resistance training is defined as a type of muscle strength-building exercise program that requires the muscle to exert a force against some form of resistance, such as weight, stretch bands, water, or immovable objects. In general, muscle-strengthening exercises can be applied through three different modes of exercise: isometric (force applied does not result in any range of motion), isotonic (resistive force remains constant), and isokinetic (velocity remains constant) exercises. With OA subjects, the most optimal strengthening exercise mode in terms of safety and efficacy should be selected in accordance with the patient's medical condition.

Previously, RCTs in patients with knee OA have showed that strengthening of the quadriceps musculature, using either isometric or isotonic strengthening exercises have increased quadriceps strength, reduced knee pain and improved function (Marks 1993, van Baar et al. 1998, Fransen et al. 2001, Huang et al. 2003). For example, after 8 weeks of isokinetic exercise, isotonic exercise, and isometric exercise in patients with moderate knee OA, Huang et al. (2003) found that each group showed significant reduction in pain and disability, and improvement in walking speed after treatment and at the one-year follow-up. Isotonic exercise had the greatest effect on pain reduction, whereas isokinetic exercise caused greatest increase in walking speed and muscle-strength gain at different angular velocities (Huang et al. 2003). The authors suggested isotonic exercises for initial strengthening in OA patients with knee pain, followed by isokinetic exercise for improving joint stability and walking endurance.

The effectiveness of isolated resistance training on arthritis symptoms, physical performance and psychological function was examined by Lange et al. in their large systematic review (Lange et al. 2008). The review included 18 moderately robust RCTs according to the Delphi methodological quality criteria list (Verhagen et al. 1998). The most common exercise modalities were dynamic

or isotonic training. Machine-based resistance training was used in almost half of the studies, and a similar proportion used free weights, elastic resistance bands or other items available at home such as stairs or chairs. Most training programs lasted from one to six months. Pain, physical performance and muscle strength all significantly improved following resistance training. The mean relative effect sizes for the strength outcomes were 0.38, ranging from -0.04 to 1.52, and thus small to moderate. The authors were critical of the fact that most of the training studies lacked documentation on the actual training intensity in relation to the prescribed training intensity, and therefore called for more research to establish dose-response relationships with respect to resistance training.

Although in the systematic review by Lange et al. (2008) mean improvement in muscle strength of 17% was rather moderate, it has also been reported that with more intensive resistance training knee OA subjects can attain higher relative strength gains (Schilke et al. 1996, Baker et al. 2001, Huang et al. 2005, Foroughi et al. 2011). For example, in the study by Baker et al. (2001), knee OA patients who participated in a high intensity home-based progressive strength training regimen showed a 71% improvement in knee extension strength in the most painful leg versus a 3% improvement in the nutrition education control group. In addition, the strength training group showed a 43% mean reduction in pain and a 44% mean improvement in self-reported physical function versus controls. On the other hand, it should be noted that the impacts are likely to be overestimated in exercise studies where exercise control groups have not been included or where the outcome measures have been self-reports of pain and function, which are highly sensitive to placebo effects (Zhang et al. 2010). Nevertheless, the results of the study by Baker et al. (2001) indicate that greater improvement in strength is due to a more intensive training regimen, and that subjects with knee OA can safely participate in high-intensity strength training. The exact mechanism whereby strength training improves symptoms in knee OA is unknown, but increased muscle strength, reduced knee pain, improved psychological well-being and self-efficacy (Singh et al. 1997, Vincent & Vincent 2012), and improved or maintained cartilage integrity (Durmus et al. 2013) have been proposed as potential factors for improving physical function and quality of life.

Aerobic exercise

Aerobic exercise can be defined as a type of physical activity that increases the heart rate and promotes increased use of oxygen in order to improve the overall condition of the body. Since people with lower limb OA often have deconditioned cardiovascular capacity, even when compared to sedentary matched controls, it is of great importance to improve OA subjects' aerobic fitness in addition to other overall health benefits. Both direct tests of maximum oxygen uptake (Mangione et al. 1999) and surrogate indicators of aerobic fitness, such as the 5-min (Peloquin et al. 1999) or 6-min walk tests (Kovar et al. 1992, Peterson et al. 1993, Bruno et al. 2006) have been used with knee OA subjects.

The 6-min walk test has been shown to have high reliability in individuals with medically diagnosed OA (Kovar et al. 1992).

Participation in the aerobic exercise programs (Ettinger et al. 1997, Minor et al. 1989, Kovar et al. 1992, Mangione et al. 1999, Bruno et al. 2006) has shown uniformly beneficial effects on aerobic capacity in OA subjects. In most aerobic exercise trials, the primary modality for exercise has been walking three times a week, which has been compared to patient education (Kovar et al. 1992, Bruno et al. 2006) or nonaerobic exercise (Ettinger et al. 1997, Minor et al. 1989). In the study by Mangione et al. (1999) among older persons with painful knee OA, the effects of high-intensity (70% heart rate reserve) and low-intensity (40% heart rate reserve) stationary cycling showed that low-intensity cycling was as effective as high-intensity cycling in increasing aerobic capacity, improving functional status and decreasing pain (Mangione et al. 1999). This is an encouraging finding showing that function and fitness can be improved even with low-intensity aerobic training in knee OA subjects who may find training at a high-intensity level too difficult or who are worried that only high-intensity training is effective. In all the aerobic exercise trials, the duration of exercise has been relatively short ranging from 6 to 12 weeks, except in the study by Ettinger et al. where the exercise period was an exceptionally long 18 months (Ettinger et al. 1997).

Mixed exercise programs

Aerobic exercise combined with other types of exercise, such as flexibility, resistance training (Hughes et al. 2004), aquatic therapy (Keefe et al. 2004) or diet (Messier et al. 2013) has been shown to decrease pain and improve aerobic capacity, as measured with maximal oxygen uptake or via the 6-min walk test, compared with non-exercising controls. For example, in the study by Messier et al. (2013) participation in combined aerobic walking and strength training and diet for 18 months provided better overall improvements in measures of pain, physical function and the 6-min walk test compared with either intervention (exercise or diet) alone (Messier et al. 2013).

Despite the positive findings of combined exercise modalities on aerobic capacity and function or pain, contradictory findings have also been reported. In a large RCT study by Callahan et al. (2008), the researchers did not find significant effects on function or physical activity after an 8-week land-based exercise program focusing on flexibility and low-resistance training performed 2 times per week. Nor were differences in knee OA subject's aerobic capacity observed in the RCT studies by Aglamis et al. (2008) or Thorstensson et al. (2005), where combinations of aerobic, strength and flexibility training over 12 and 6 weeks, respectively, were applied. However, all these studies, except the study by Thorstensson et al. (2005), improved knee pain. Hence, it is possible that even a rather short-term multicomponent exercise program or program which is carried-out with low-intensity training may have a favorable effect on pain, although not on aerobic fitness. However, in the recent systematic review by Juhl et al. (2014), the authors suggested that for the best results in knee OA

treatment, exercise programs should focus either on resistance training or aerobic training rather than using a mix of different exercise types.

Although aquatic exercise per se is not purely a mixed exercise program, it is addressed here since it involves a variety of exercise components with different emphases on strengthening, flexibility and endurance (Bennell et al. 2011). Aquatic therapy in the treatment of knee OA is often chosen as an alternative strategy for land-based exercise if the subject is unable to train on land due to pain or physical disability (Batterham et al. 2011). It is thought, although not proven, that the characteristics of water of warmth, reduced loading on the joint due buoyancy, resistance to movement and equal pressure to joint protect the knee joint and allow more efficacious training. To date, five systematic reviews have been published on the effects of aquatic training on lower limb OA (Bartels et al. 2007, Batterham et al. 2011, Waller et al. 2014, Quintrec et al. 2014, Lu et al. 2015). In most cases, the meta-analyses of these systematic-reviews have been conducted on both knee and hip joint studies, since it is often clinically difficult to define patient groups having knee or hip OA only, and since the exercise studies described are not specific to the knee or hip, but to both joints (Bartels et al. 2007). The systematic reviews by Bartels et al. (2007), which included six combined hip and knee OA trials with total of 800 participants, and that by Waller et al. (2014), which included 11 combined hip and knee OA trials with total of 1092 participants, compared the effectiveness of aquatic exercise in relation to other interventions or no intervention. The results of these meta-analyses showed, in favor of aquatic exercise, a small effect size (ES) in pain (range 0.19 - 0.26), from a non-statistically significant difference to a small ES in stiffness (0.20, 95% CI 0.03, 0.36), a small ES in function (range 0.22 - 0.26) and from a small to moderate ES in quality of life (range 0.24 - 0.32). These effects were noticed immediately after the end of treatment, with an average treatment duration of three months, and were no longer present at the six month follow-up. In the meta-analysis by Waller et al. (2014) investigating the effect of aquatic exercise on knee OA only (three trials), no significant effects were demonstrated.

In their systematic review, Batterham et al. (2011) demonstrated that both aquatic exercise and land-based exercise have similar effects on the outcomes of function and mobility. 10 RCTs among participants with OA or rheumatoid arthritis, or both were included in the meta-analysis. The authors stated that neither the aquatic nor land-based exercise environment appeared to be superior to the other (Batterham et al. 2011). Similarly, in their systematic review of five RCTs on aquatic exercise with a total of 457 patients, Quintrec et al. (2014) found that aquatic exercise was as effective as land-based exercise on pain and function in hip and knee OA in very old patients (Quintrec et al. 2014). Also, in the very recent systematic review by Lu et al. (2015), the effects of aquatic exercises were compared with land-based exercise or non-exercise. Six RCTs with a total of 398 participants were included in the systematic review. The authors found a moderate effect on physical function in favor of aquatic exercise (standardized mean difference [SMD] -0.55; 95% CI -0.94 to -0.16), but

no evidence for pain or quality of life. The authors concluded that aquatic therapy is safe and can be considered as an adjuvant treatment for patients with knee OA. However, high quality studies appear to be lacking and the existing studies are too short-term to provide further recommendations on how to apply this therapy.

2.2.5 Effects of exercise on knee cartilage

Previously, because the effects of exercise on human articular cartilage were difficult to investigate directly, cartilage responses to exercise were explored in animal models. In a set of studies conducted on Beagle dogs, running exercise of 4 km/day on a treadmill, five days a week, for 15 weeks increased thickness and PG content in the femoral cartilage, whereas collagen content was unaltered (Kiviranta et al. 1988, Säämänen et al. 1994). Using the same animal model running exercise for 20 km/day did not improve the biomechanical properties of articular cartilage (Jurvelin et al. 1990), but running exercise for 40 km/day reduced the stiffness of articular cartilage (Arokoski et al. 1994) although it did not change the overall PG content (Visser et al. 1998). By contrast, Radin et al. (1982) found cartilage fibrillation, decreased PG content, and subchondral changes in sheep subjected to four hours' walking daily on a hard surface over two and a half years (Radin et al. 1982). Earlier, Dekel & Weissman (1978) found in rabbit knee articular cartilage that overuse caused by a driving wheel alone did not produce OA, but when combined with axial peak overloading, osteoarthritic changes were observed (Dekel & Weissman 1978). Study of the relationship between exercise, aging and cartilage, including the responses of the collagen network and GAG content in young and mature guinea-pigs following a treadmill running regime of 2.5 km/day 5 days a week for 15 weeks, showed that the exercise strengthened the superficial articular collagen network in the young runners, while it weakened the property of the collagen network in older animals (Hyttinen et al. 2001). In these animals, no significant changes in cartilage GAG content either in the young or adult mature guinea-pigs were observed. In a lifelong study of C57BL mice, moderate running (1 km/day) on a treadmill between 2 and 18 months of age increased the incidence and severity of OA in the knee joints (Lapveteläinen et al. 1995). However, in the study on beagle dogs with normal joints, lifelong regular treadmill exercise at 3 km/h for 75 minutes 5 days a week for 527 weeks while wearing a jacket weighing 130% of their body weight showed no evidence of knee cartilage injury (Newton et al. 1997). Based on these animal experiments, it seems that moderate and even rather strenuous physiological joint-loading does not cause harm to the articular cartilage. However, overuse with time may jeopardize the ability of the articular cartilage to maintain its normal structural and functional properties. Direct generalizations from animal studies to human physiology should, however, be made with caution. For instance, the articular cartilage turnover in rodents is complicated since the growth plate of these animals remains present and is at least partly metabolically active even in older age (Nilsson et al. 2002).

Currently, quantitative magnetic resonance imaging techniques provide noninvasive biomarkers for the estimation of exercise induced biomechanical changes in human and animal articular cartilage. In a longitudinal analysis using the dGEMRIC technique Van Ginckel et al. (2010) showed that dGEMRIC indices in young novice female runners with asymptomatic knees were significantly higher after a 10-week running training program than those in the sedentary control group. Also, the study by Roos & Dahlberg (2005) showed significant positive change in the mean dGEMRIC index after a moderate 4-month weight-bearing exercise program in post-meniscectomised middle-aged subjects. These studies are supported by the cross-sectional study by Tiderius et al. (2004) showing that the dGEMRIC index, reflecting the PG content of cartilage, was higher in physically active individuals, suggesting an adaptive capacity of human knee cartilage.

Exercise induced changes on knee cartilage morphology have been also studied by using conventional MRI. In the study by Cotofana et al. (2010), the authors did not find any significant differences in patellar or tibiofemoral knee cartilage volume or thickness after three months of endurance or strength training in untrained middle-aged women (Cotofana et al. 2010). However, in a study targeting on patellofemoral compartment, Teichtal et al. (2009) found that vigorous physical activity over 2 years was associated with a reduction in patella cartilage loss for men and women without pre-existing cartilage damage, but not for people with baseline cartilage defects (Teichtahl et al. 2009). This finding by Teichtal et al. (2009) is supported by the cross-sectional study of Wijayaratne et al. (2008), in which fortnightly participation in exercise tended to be associated with a reduction in the annual rate of patella cartilage volume loss (Wijayaratne et al. 2008). These research findings related to the patellofemoral cartilage indicate that regular exercise is beneficial for cartilage volume. The different responses in patellofemoral and tibiofemoral compartments due to exercise participation may be partly caused by the different biomechanics of these joints, i.e., shear versus impact loading. The forces on the patellofemoral compartment during physical activities are not as strenuous and compressive as the forces on the tibiofemoral compartment (Taylor et al. 1998).

There are also studies on the biochemical markers of molecular changes in the extracellular matrix of cartilage, synovial metabolism and subchondral bone due to exercise programs. To name a few, cartilage oligometric matrix protein (COMP) (Andersson et al. 2006), keratan sulfate (KS) and hydroxyproline, markers of cartilage degradation (Bautch et al. 1997), interleukin 6, tumor necrosis factor and C-reactive protein, markers of chronic inflammation (Nicklas et al. 2004), transforming growth factor-beta 1 (TGF-β1), an anabolic marker of cartilage, hyaluronan (HA), a marker of synovial inflammation (Chua et al. 2008) and bone GLA protein, a marker of bone formation (Bellometti et al. 2002) have been used to determine the effects of exercise on knee joints with OA. Overall, the evidence indicates that exercise programs in subjects with knee OA do not induce long-term changes in biochemical joint composition (Bennell et al. 2011). On the other hand, it should be noted that circulating levels of

biomarkers measured in serum or urine may also be affected by other metabolic events than those originating solely from the affected joint (Bennell et al. 2011).

2.2.6 Simultaneous effects of exercise on bone and cartilage

In humans, the effects of intensive weight-bearing loading have not thus far been examined simultaneously on bone and articular cartilage. Instead, one animal experiment has reported on the effects of long-term running on articular cartilage and bone mass in ovarectomized (OVX sedentary and OVX + run) and non-ovarectomized rats (non-OVX sedentary and non-OVX + run) (Chang et al. 2010). After a 9-month treadmill running regime, the rats in the OVX group had more intact cartilage, although lower bone mass than the non-OVX control rats. The study implies that weight-bearing exercise protects cartilage but it does not necessarily hinder the bone loss observed after menopause (Chang et al. 2010). However, it should be once again noted that results from animal models cannot be generalized directly to humans, since surgically induced ovarectomy and the subsequent post-menopausal-like state does not necessarily closely resemble the natural degeneration of human cartilage. Nevertheless, given the lack of human studies, further investigation of the effects of intense weight-bearing loading simultaneously on bone and cartilage is warranted both in human and animal studies.

2.3 Summary of the literature

Targeted exercise interventions have shown that exercise can significantly improve bone health in all age groups; e.g., in children (Heinonen et al. 2000, Nikander et al. 2010), premenopausal women (Babatunde et al. 2012), postmenopausal women (Uusi-Rasi et al. 2003, Polidoulis et al. 2012) and elderly women (Karinkanta et al. 2007). Although exercise during childhood and adolescence is more efficacious for bone than exercise started in adulthood (Kannus et al. 1995), studies have shown that aerobics, weight-bearing, and resistance exercises have positive effects on BMD of the spine, as does walking on hip BMD, among postmenopausal 45- to 70-year-old women (Bonaiuti et al. 2002). Overall, the most osteogenic exercise form should include high-impact loading with rapid versatile movements (Taaffe et al. 1997, Sievänen 2012). Whether this mode of impact exercise is also optimum for postmenopausal women is equivocal, since according the meta-analysis investigating the effects of differing impact exercise protocols on postmenopausal women's BMD, bone strength increased with combined loading protocols and low-impact protocols but not with high-impact loading protocols (Martyn-St James & Carroll 2009). In addition to bone mineral mass or density enhancement, exercise is beneficial for the prevention of falls and osteoporotic fractures among older adults (Gregg et al. 2000, Chang et al. 2004, Karinkanta et al. 2010).

Currently, since no treatments are available that can heal and improve OA articular cartilage, the main treatment goal is to relieve symptoms and prevent OA progression. Of the non-pharmacological interventions, exercise therapy has shown to be beneficial in reducing pain and improving physical function and quality of life, although the overall treatment effects have been found to be small to moderate (Fransen et al. 2015). Unfortunately, the beneficial effects of exercise decline over time and finally disappear when exercise is stopped (van Baar et al. 2001). The optimum exercise modality in the treatment of knee OA is not known, but aerobic conditioning and resistance training may be suitable for people with OA (Bennell et al. 2011). Also, aquatic exercise may be a good alternative to land-based exercise, especially in subjects with advanced OA (Batterham et al. 2011, Quintrec et al. 2014).

An aspect missing from the exercise interventions in subjects with knee OA is the detection and monitoring of the effects of exercise on the articular cartilage. The novel advanced qMRI techniques of dGEMRIC and T2 relaxation time offer biomarkers to track cartilage quality in clinical trials (Matzat et al. 2013). These methods have been applied in some human studies with promising results, suggesting that adult human cartilage has the potential for exercise adaptation through increased cartilage GAG content (Roos & Dahlberg 2005, Van Ginckel et al. 2010). However, there is a paucity of literature on this topic in subjects with established knee OA.

3 PURPOSE OF THE STUDY

The main purpose of this thesis was to examine the effects of a 12-month high-impact exercise program on bone and articular cartilage properties in postmenopausal women with mild knee OA (Studies III and IV). In addition, the relationship between knee OA and femoral neck bone structural characteristics in postmenopausal women with and without mild knee radiographic OA was studied (Study II). Moreover, before the start of the exercise intervention the reproducibility of measuring cartilage by delayed gadolinium-enhanced MRI (dGEMRIC) was determined in healthy asymptomatic subjects (Study I).

The specific research questions were:

1. Is the dGEMRIC measurement reproducible at different knee joint surfaces in healthy subjects? (Study I)
2. Is there an inverse relationship between knee OA and femoral neck bone structural characteristics in postmenopausal women with and without radiographic OA? (Study II)
3. Does a 12-month high-impact training program increase femoral neck bone mineral mass and strength, and enhance the biochemical composition of knee cartilage in postmenopausal women with mild knee OA? (Studies III and IV)

4 MATERIAL AND METHODS

4.1 Study design, setting, and participants

This doctoral thesis comprises data from methodological, cross-sectional and RCT studies, with a total of 102 participants. Participants were recruited from the Central Finland area, and the project was conducted between March 2007 and April 2010 in the facilities of the Department of Health Sciences at the University of Jyväskylä.

A methodological test-retest study, titled "dGEMRIC reproducibility" was conducted to assess the reproducibility of measuring cartilage in the knee joint by delayed gadolinium-enhanced MRI (dGEMRIC). Subjects were healthy asymptomatic young adults. A RCT titled "Training intervention" investigated the effects of exercise on bones, cartilage, symptoms and physical function. The participants in this RCT were postmenopausal women with mild knee OA. A cross-sectional study titled "Bone and cartilage associations" examined bone and cartilage characteristics in postmenopausal women with and without mild knee OA. The study designs, participants, and main outcomes are summarized in Table 1.

4.1.1 dGEMRIC reproducibility (Study I)

The day-to-day reproducibility of the measurement of cartilage at different knee cartilage surfaces by delayed gadolinium-enhanced MRI (dGEMRIC) was measured by a 1.5 Tesla scanner. The volunteers for this test-retest study were recruited by brochures distributed in the University of Jyväskylä. The eligibility criteria for the study were: healthy, age ≥ 18 years, no knee-related symptoms, and no history of knee injury or surgery. A participant was excluded if she or he had contraindications to MRI, allergies to contrast agents, congestive heart failure, claustrophobia, or if she was pregnant or breastfeeding. After the participants' eligibility was confirmed by interview, and conventional MRI diagnostic series were performed to exclude subjects possibly having knee joint

structural damage, five females and five males met the criteria for entry to the study. The dGEMRIC experiment was repeated three times with an average interval of 5 (SD 3) days between imaging sessions.

TABLE 1 The summary of the thesis material, participants, and main outcomes.

Study	**Data**	**Design**	**Participants**	**Age,** range, years (Mean ± SD)	**Main outcomes**
I	dGEMRIC reproducibility	Methodological - Test-retest	10 asymptomatic volunteers Young women (n = 5) and men (n = 5)	25 - 47 (32 ± 6)	• dGEMRIC index accuracy in different knee cartilage regions
II	Bone and cartilage associations	Cross-sectional	90 postmenopausal women Mild osteoarthritis, n = 78 Non-osteoarthritis, n = 12	50 - 66 (58 ± 4)	• Femoral neck BMC, Z and CSA • Tibiofemoral joint T2 and dGEMRIC index
III - IV	Training intervention	RCT	80 postmenopausal women Exercise group, n = 40 Control group, n = 40	50 – 66 (58 ± 4)	• Femoral neck, trochanter and lumbar spine BMC • Femoral neck Z, CSA and W • Tibiofemoral joint dGEMRIC index and T2 • Knee symptoms • Physical function scores • Physical activity data

SD = Standard deviation, dGEMRIC = delayed gadolinium-enhanced MRI of cartilage, BMC = Bone mineral content, Z = section modulus, CSA = Cross-sectional area, T2 = T2 relaxation time, RCT = Randomized controlled trial, W = Width

4.1.2 Training intervention (Studies III - IV)

This study was a randomized controlled trial (ISRCTN58314639) investigating the effects of a 12-month high-impact training program on bone mineral content, estimated biochemical composition of cartilage, physical function and knee-related symptoms in postmenopausal women with mild knee OA. The voluntary participants for this study were recruited through a newspaper advertisement from the Jyväskylä region in Central Finland. A total of 298 women responded and after assessing their eligibility by telephone interview, 208 women were invited for knee X-rays. After the knee X-rays, dual-energy X-ray absorptiometry (DXA) and clinical examinations were conducted with the 80 subjects meeting the inclusion criteria, and the baseline measurements were performed. The recruitment process of the participants and the study flow is presented in Figure 6 as a training intervention.

Eligibility criteria were: postmenopause, age 50 – 65 years, knee pain on most days, regular intensive exercise no more than twice a week, no illnesses that contraindicated exercise or would limit participation in the exercise program and a Kellgren and Lawrence (K/L) radiographic tibiofemoral joint OA grade 1 - 2. Exclusion criteria were: T-score for femoral neck bone and lumbar spine mineral density (BMD, g/cm^2), measured with dual-energy X-ray absorptiometry, lower than -2.5 (i.e., indicating osteoporosis), body mass index (BMI) ≥35 kg/m^2, knee instability or surgery of the knee due to trauma, joint replacement, inflammatory joint disease, intra-articular steroid injections in the knee during the preceding 12 months and contraindications to MRI (allergies to contrast agents or renal insufficiency).

After the baseline measurements just before initiation of the exercise intervention, the participants were randomly assigned into the exercise group (n = 40) or the control group (n = 40). The random allocation was done by a statistician outside of the research group and blinded to the study participants. The randomization was done according to a computer generated, blocked randomisation list. A block size of 10 was used, stratified according to K/L grade 1 and 2.

4.1.3 Bone and cartilage associations (Study II)

The purpose of this study was to evaluate the association between knee OA severity given as K/L grades from 0 to 2 and (i) femoral neck bone traits, and (ii) knee cartilage biochemical composition in women with and without radiographic knee OA. In order to get participants without knee OA, an age-, weight-, and height-matched sample of women with no knee symptoms was recruited in addition to the Training intervention participants. Participants without knee OA were recruited via e-mail advertisements from predominantly female work places in the Jyväskylä region. A total of 41 women expressed their initial interest in the study, and their willingness and eligibility were determined in a telephone interview. The inclusion and exclusion criteria were same as for the Training intervention participants except that the women

without knee OA should not have had any previous knee pain or knee-related physical disability. Their suitability for the study was confirmed by radiographs, and only subjects who had no radiographic OA changes (*i.e.,* K/L grade 0) in both tibiofemoral joints were entered in the study. Of the 32 radiographed volunteers, 12 were applicable in the study. These 12 women underwent the same outcome measurement protocol, including DXA scannings, as was previously implemented at baseline with the Training intervention participants. The recruitment of the asymptomatic postmenopausal women without knee OA (hereafter called K/L 0 group) is described in Figure 6, under the heading "additional recruitment". Data assembled from the measurements of the K/L 0 group and from the baseline measurements of the postmenopausal women with mild knee OA (K/L 1-2) in the RCT formed the data used in this cross-sectional study.

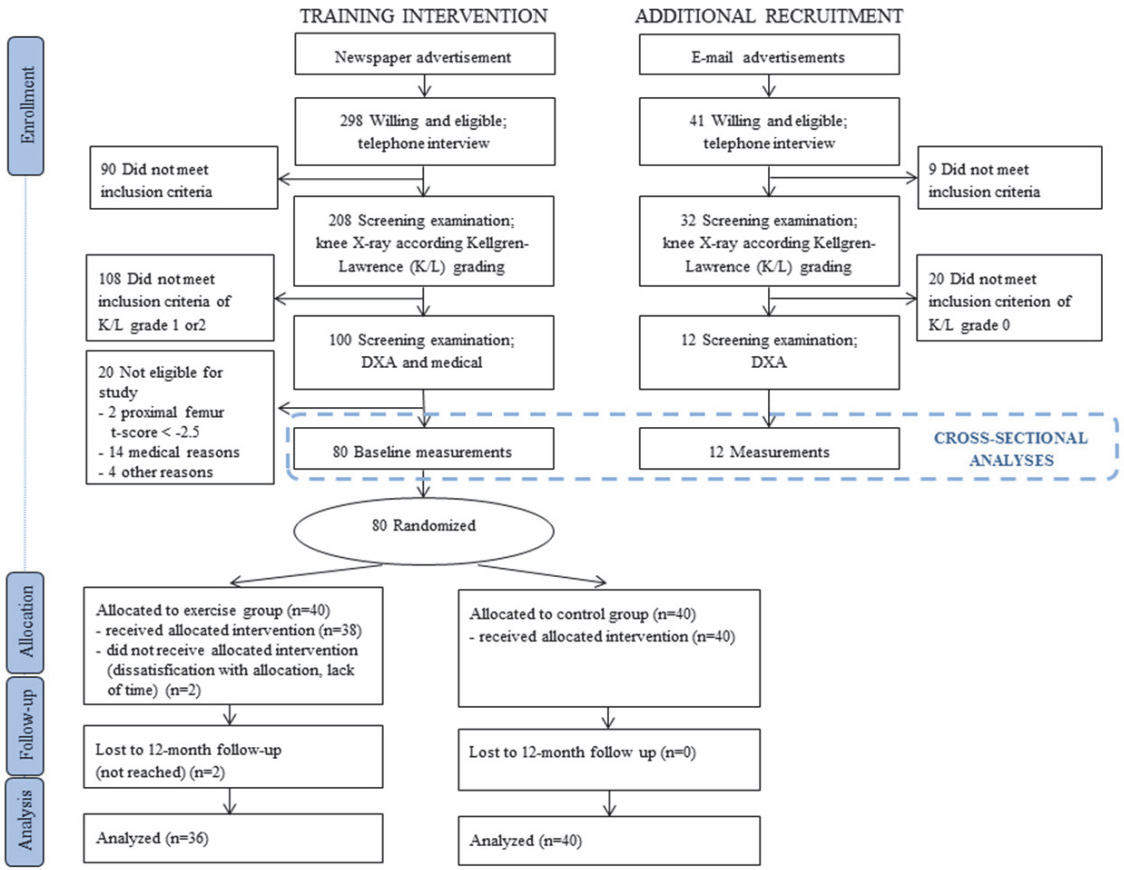


FIGURE 6 Flow chart of the studies.

4.2 Ethics

All study protocols were approved by the Ethics Committee of the Central Finland Health Care District (journal numbers 1/2007, 1E/2008 and 9/2009 for the training intervention amendment to the additional recruitment protocol). The Training intervention study protocol conformed to the principles of the Declaration of Helsinki, and study was registered in the controlled trials database (ISRCTN58314639). In each study, all participants were fully informed about the measurement procedures and possible risks involved. Written informed consent was obtained from all participants prior to study.

4.3 Measurements

All the outcome measurements along with their reliability values are listed in Table 2. All measurements and analyses were conducted in a blinded manner, except those by JM (author of the dissertation) who, as a PhD student, had multiple roles in designing and conducting the studies, collecting and analysing the data and writing the manuscripts.

4.3.1 Bone measurements

Bone mineral content (BMC, g) of the femoral neck (Studies II and III) and trochanter from the side with the higher K/L grade knee and lumbar spine (L2 - L4; Study III) was measured with dual-energy X-ray absorptiometry (DXA, GE Medical Systems, Lunar Prodigy, Madison, WI, USA). In addition, femoral neck bone mineral density (BMD, g/cm^2) T-score (<-2.5) was used as an exclusion criterion (Studies II, III and IV). The precision of the bone trait outcome measurements are summarized in Table 2.

In addition, femoral neck cross-sectional area (CSA, [mm^2]; Studies II and IV), subperiosteal width (W, [mm], Study IV) and the section modulus (Z, [mm^3], as an index of bending strength; Studies II and IV) were analyzed and calculated with advanced hip structural analysis (AHA) as per manufacturer's software (Beck et al. 1990, Beck 2007). In a K/L 0 group, the average of both femoral neck sites was used in the analysis (Study II).

TABLE 2. Measurement methods used in this doctoral dissertation and their reliabilities.

Outcome	Paper	Method and reference	Reliability and reference
BONE TRAIT			
Bone mineral content (BMC), g	II, III	DXA	CV 0.9%(Sievänen et al. 1996)
Bone mineral density (BMD), g/cm^2	II - IV	DXA	CV 0.8% (Sievänen et al. 1996)
Section modulus (Z), mm^3	II, IV	DXA derived AHA (Beck et al. 1990)	CV 0.7% (Sievänen et al. 1996)
Cross sectional area (CSA), mm^2	II, IV	DXA derived AHA (Beck et al. 1990)	CV 3.1% (Hind et al. 2012)
Width (W), mm	IV	DXA derived AHA (Beck et al. 1990)	CV 0.2% (Sievänen et al. 1996)
CARTILAGE TRAIT			
dGEMRIC index, ms	I - IV	Delayed Gd(DPTA)$^{2-}$ -Enhanced MRI (Bashir et al. 1996)	N.A.
T2, ms	II - IV	T2 relaxation time (Xia 1998)	CV 5% (Hannila et al. 2009)
PHYSICAL FUNCTION			
Dynamic balance and agility[a], s	II, III	Figure-of-eight running test (Tegner et al. 1986)	ICC 0.90 (Vartiainen et al. 2006)
Isometric knee extension force, N	II, III	Isometric dynamometer	CV 6.3% (Sipilä et al. 1996)
Isometric knee flexion force, N	II, III	Isometric dynamometer	CV 8.5% (Sipilä et al. 1996)
Leg extension power, W	II, III	Counter movement jump (Rantalainen et al. 2010)	CV 3.6% (Rittweger et al. 2004)
VO_{2max}, mL ·/kg/min	II, III	2-km walk test (Oja et al. 1991)	ICC 0.87 (Rance et al. 2005)
PHYSICAL ACTIVITY			
Exercise loading	III, IV	Accelerometer-based body movement monitor (Jämsä et al. 2006)	CV 4.0% (Vihriälä et al. 2003)
Daily physical activity	III, IV	Body movement monitor (Jämsä et al. 2006)	CV 4.0% (Vihriälä et al. 2003)
Total physical activity loading	IV	Body movement monitor (Ahola et al. 2010)	
Habitual physical activity	II, III	Questionnaire (Ainsworth et al. 2011)	
HEART RATE	III	Portable heart rate monitor	N.A.
RATE OF PERCEIVED EXERTION	III	Borg scale (Borg 1982)	ICC 0.92 (Leung et al. 2004)

TABLE 2. (continues)

Outcome	Paper	Method and reference	Reliability and reference
CLINICAL SYMPTOMS		WOMAC (Bellamy et al. 1988)	(Soininen et al. 2008)
knee pain	II, III	Pain subscale	ICC 0.92
knee stiffness	II, III	Stiffness subscale	ICC 0.80
functional limitation	II, III	Functional limitation subscale	ICC 0.92
QUALITY OF LIFE	IV	RAND-36 questionnaire (Hays et al. 1993)	Bland-Altman 0.8 (Brazier et al.1992)
ADVERSE EVENTS	II	Questionnaire devised by the research group	N.A.
GENERAL HEALTH	II, III	Questionnaire devised by the research group	N.A.

DXA = dual-energy X-ray absorptiometry, AHA = Advanced Hip Structural Analysis, N.A. = not available, ICC = Intra-class correlation coefficient, CV = coefficient of variation, VO_{2max} = estimated maximal oxygen uptake, WOMAC = Western Ontario and McMaster Universities Arthritis Index, RAND 36 = health-related quality of life questionnaire

[a]Negative number indicates better balance.

4.3.2 Cartilage measurements

T2 and the dGEMRIC index, i.e., spin lattice relaxation time (T1) in the presence of gadolinium diehylene triamine pentaacetic acid (Gd $[DTPA]^{2-}$) ions were determined using a Siemens Magnetom Symphony Quantum 1.5 T scanner (Siemens AG, Medical Solutions, Erlangen, Germany) with a standard transmit/receive knee array coil. The participants were imaged lying supine with knees supported in a fixed position. In the subjects with radiographic knee OA, scans were performed on the side with the higher K/L grade knee (Studies II - IV) and from side of the right knee with the healthy volunteers (Study I) and postmenopausal women without radiographic knee OA (Study II). T2 mapping, which was performed prior to the dGEMRIC experiment, was carried out using a sagittal multislice, multiecho, fast-spin echo sequence (field of view [FOV] 140 mm, acquisition matrix 256 × 256, repetition time [TR] 2090 ms, eight echo times [TE] between 13 and 104 ms, echo train length [ETL] 8, 3-mm slice thickness). The slices were positioned perpendicular to a line tangential to the posterior femoral condyles in the axial scout view. The centermost slices of both medial and lateral femoral condyles were chosen for the analyses.

For the dGEMRIC imaging, a double dose, i.e., 0.4 mL/kg (0.2 mM/kg), intravenous administration of Gd-DTPA2- (Magnevist, Schering, Berlin) was followed by 15 min of light knee exercises in order to enhance the penetration of contrast agent into knee cartilage. Ninety minutes after the injection, T1 mapping was performed in the sagittal plane using a single slice inversion recovery fast-spin echo sequence (FOV = 14 cm, matrix 256 × 256, TR = 1800 ms, TE = 13 ms, six inversion times [TI] between 50 and 1600 ms, 3-mm slice thickness). The dGEMRIC slices were positioned similarly as in the T2 imaging. The remaining slice was then positioned at the center of the medial and lateral condyles as viewed on the axial scout image (Studies II - IV). The dGEMRIC reproducibility (Study I) protocol was similar to that used with the postmenopausal women, except that only the lateral side of the tibiofemoral compartments and, on the axial plane, also the patellofemoral compartment, was scanned. From the patellofemoral slices the most central slice of patella was chosen for the analyses.

For the analyses cartilage was manually segmented using in-house software under Matlab application (Mathworks, Inc. Natick, MA, USA) by drawing the entire visible cartilage of the femur, tibia (Studies I - IV) and patella (Study I), and by dividing them into different topographical locations according to a scheme modified from Eckstein et al. (2006b). Moreover, in the dGEMRIC reproducibility study, each segment was further divided into separate regions-of-interest (ROIs) for the superficial and deep halves of cartilage thickness. The segmentation was carried out by two accredited members of the study group, whose inter-observer error (CV_{RMS}) for T2 full-thickness ROIs was on average 2% and 3% for dGEMRIC. Means and standard deviation of dGEMRIC indices and T2 relaxation times were calculated for full-thickness in weight-bearing femoral and tibial cartilages (Studies II - IV), whereas means and SDs were given for the

entire cartilage at each joint, as well as for all the topographical full-thickness, deep and superficial cartilage ROIs in the dGEMRIC reproducibility study. Except for the reproducibility study, all dGEMRIC values were corrected by body mass indices (BMIs), as suggested by Tiderius et al. (2006).

4.3.3 Physical function measurements

Dynamic balance and agility was tested with a standardized figure-of-eight running test (Studies II and III). The test was originally developed to evaluate dysfunction and success of rehabilitation after an anterior cruciate ligament injury of the knee (Tegner et al. 1986), and has been modified for older adults by adding an extra lap (Heinonen et al. 1996, Carter et al. 2002, Uusi-Rasi et al. 2003, Karinkanta et al. 2007). In the test, two poles were placed 10 meters apart. The participant was asked to run (or walk) from a standing start two laps of the course as fast as possible. The running time was measured using photoelectric-cells. After one practice trial, the best of two attempts (shortest performance time) was chosen for analysis.

Maximal isometric knee extension and flexion forces (Newton, N) were measured in both legs using an adjustable computer-linked dynamometer chair (Good Strength, Metitur Ltd, Palokka, Finland; Studies II and III). For all participants, the leg that was measured first was randomly chosen. This ensured that the known tendency to perform better on the later measurements randomly hits the affected or non-affected knee side. During the measurements, the knee was set at an angle of 60° from full extension with the ankle fastened with a belt above the malleolus to a strain gauge. After three practice trials, four maximal efforts, separated by a 30-second rest interval, were conducted until no further improvement occurred. The best trial was accepted as the result, and the average of the best attempts from both legs was calculated for the analysis.

Leg extension power was measured with a custom-made force plate (University of Jyväskylä, Finland) during a vertical counter movement jump (Studies II and III). The participants were instructed to jump with hands on hips as high as possible with their preferred counter movement depth and velocity. After two to five practice trials, three maximal jumps, separated by a 30-second rest interval, were conducted and the best recorded trial was chosen for the analysis. Power was examined by measuring peak instantaneous power production during the takeoff phase in watts. Results were analyzed from the vertical ground reaction force using a custom-made Matlab script. Peak instantaneous power was extracted as we have described in detail previously (Rantalainen et al. 2010).

Aerobic fitness was assessed with a standardized 2-km walk test (UKK Institute, Finland; Studies II and III). The test measures aerobic capacity indirectly (Oja et al. 1991). The oxygen consumption at maximum exertion $VO2_{max}$ ($mL \cdot kg^{-1} \cdot min^{-1}$) was predicted by an equation according to walking time, heart rate at the finish line and, in addition, age, gender and BMI. Heart rate was measured by a portable heart-rate monitor (Polar F6, Polar Electro Ltd, Kempele, Finland).

4.3.4 Knee-related symptoms

Perceived pain, stiffness, and self-rated physical functional difficulty were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire (Studies II and III). The WOMAC is a three-dimensional, disease-specific, self-administered health status instrument developed to quantify intervention effects of the hip or knee OA treatment (Bellamy et al. 1988). A visual analogue scale (VAS, 0 - 100 mm) format was used, where higher scores on VAS indicate a higher degree of joint pain, joint stiffness and functional limitation. The pain subscale consists of 5 items, the stiffness subscale of 2 items, and the functional limitation subscale of 17 items. The scores for each subscale were normalized, by multiplying the sum of the raw scores of the items in each dimension by the correction factor.

4.3.5 Descriptive background characteristics

Knee status. In the postmenopausal women with mild knee OA (Studies II - IV) and K/L 0 group (Study II) the severity of radiographic knee OA was evaluated by a musculoskeletal radiologist. The radiographs were acquired from both knees in screening examinations with a postero-anterior view of the tibiofemoral joint in a semi-flexed weight-bearing position. A tibiofemoral joint OA severity of grade 0 (none), 1 (doubtful narrowing of joint space, possible osteophytes) or 2 (definite joint space narrowing and osteophytes) was determined according the K/L classification (Kellgren & Lawrence 1957). In participants with radiographically confirmed OA, the final grade was the highest (either 1 or 2) for the most severely-affected knee.

Health status. General health and habitual physical activity were assessed at baseline by a questionnaire devised by the research group. A health questionnaire addressed medical conditions, current medications, anamnestic records of gynecology and knee OA, a multivitamin supplement intake, and current leisure time physical activity (Studies II - IV). Baseline physical activity was converted into metabolic equivalent task (MET)-hours per week according to a scheme modified from (Ainsworth et al. 2011) (Studies I - IV). In addition, in order to ensure that the participants would not have any potential contraindications for safe participation in the measurements and training, a structured general medical examination with detailed structured examination of the knees was performed by the attending physician (Studies III and IV).

Anthropometry. Body height and body mass were measured in all participants (Studies I - IV) in our laboratory using standard procedures, and body mass index calculated as mass (kg) divided by height (m) squared.

Health-Related Quality of Life (HRQoL). HRQoL was assessed at baseline (Study IV) using the Finnish validated version of the RAND 36-Item Short–Form Health Survey (RAND-36) (Aalto et al. 1999). The RAND-36 is a generic questionnaire comprising 8 multi-item dimensions: general health, physical functioning, mental health, social functioning, energy, pain, and physical and

emotional role functioning. Each dimension is scored from 0 to 100, with higher scores representing better HRQoL (Hays et al. 1993).

Physical activity. Daily physical activities were recorded in all participants at four and ten months from intervention start for three consecutive days by recording the number and intensity of acceleration peaks (impacts) using an accelerometer-based body movement monitor (Newtest, Oulu, Finland; Studies III and IV). During the three-day measurements, the participants wore the monitor attached to a waist belt while performing normal day-to-day activities (intervention training classes not included). The monitor was taken off at bedtime or in situation where it might get wet. The participants were also asked to keep a log indicating when the monitors were worn and removed. The number of peaks was divided into 32 different acceleration level bins (0 to 9.3) and the number of impacts in each acceleration level bin was calculated. A daily impact score was calculated for daily physical activity according to (Ahola et al. 2010) using the logarithmic relationship (DIS_{Log}) between the loading numbers and magnitude as expressed in the following equation:

$$DIS_{Log} = \sum_{i=1}^{32} (a_i + 1) ln(N_i + 1)$$

where a_i = the higher cutoff of the i^{th} acceleration level bin and N_i = number of acceleration peaks within the i^{th} acceleration level bin. One was added to the acceleration measured with the accelerometer-based body movement monitor in the DIS_{Log} calculations, since the accelerometer gives 0 g while standing still, whereas the muscles still have to counteract the 1 g caused by gravitation. The total physical activity loading index, DIS_{Total}, was calculated to describe participants' total physical activity over the study period by summing the loadings of daily physical activity and the exercise classes. For the control participants the DIS_{Total} = DIS_{Log}, since they were not involved in the exercise intervention.

In addition, throughout the study period all participants kept a diary recording the type, frequency, intensity and duration of their habitual physical activities (PA). Reported habitual PA was determined as activity that was carried out on a regular basis at least once a week with a minimum duration of 20 minutes. The participants mailed the habitual PA diaries to the research personnel monthly, and the gathered habitual PA data was converted into MET-hours per week according to a scheme modified from (Ainsworth et al. 2011) (Study IV).

4.4 High-impact exercise program

4.4.1 The training protocol

The training program consisted of modified aerobic and step-aerobic jumping exercise programs based on previous bone favorable exercise studies among premenopausal (Heinonen et al. 1996), postmenopausal (Uusi-Rasi et al. 2003), and elderly women (Karinkanta et al. 2007). The target training frequency was three times a week for 12 months, making a total of 156 exercise sessions for each trainee during the one-year intervention. All exercise classes were supervised by exercise instructors who were experienced in exercise guidance, and who had been recently trained to supervise this specific exercise program. The instructors also kept an attendance record for each of the participants.

Each exercise class included a 15 minute warm-up, 25 minutes of multidirectional high-impact exercises (effective part) and 15 minutes of cooling down (non-impact exercises and stretching). The effective part of the exercise classes comprised an aerobic jump program and a step-aerobic program, which were administered at alternating intervals of two weeks each. Both programs included, in addition to jumps, accelerating and decelerating through forwards and sideways movements with stops and turns to music. During the first 3 weeks of the aerobic and step-aerobic programs, the trainees accustomed themselves to jump training. During these periods no equipment was used. Thereafter, the magnitude of the joint loading level was gradually increased in the aerobic jumping exercises by raising the height of the foam fences from 5 to 20 cm (5 cm per 3-month period). In the step-aerobic program, the magnitude of joint loading was similarly increased by increasing the height of the step benches from 10 cm, the lowest possible, to 20 cm. The bench height of 20 cm, starting from the beginning of the third period, was retained during the fourth (last) period. The numbers of jumps performed in the aerobic exercise periods were 208 in the orientation period, 168 in the first period, 180 in the second period, 192 in the third period and 160 in the fourth period. The corresponding numbers of jumps in the step-aerobic exercise periods were 216, 192, 180, 192 and 164. The progressiveness of the aerobic jump program and step-aerobic program expressed as the number of jumps and heights of the jumping obstacles and step-benches in each period is shown in Figure 7.

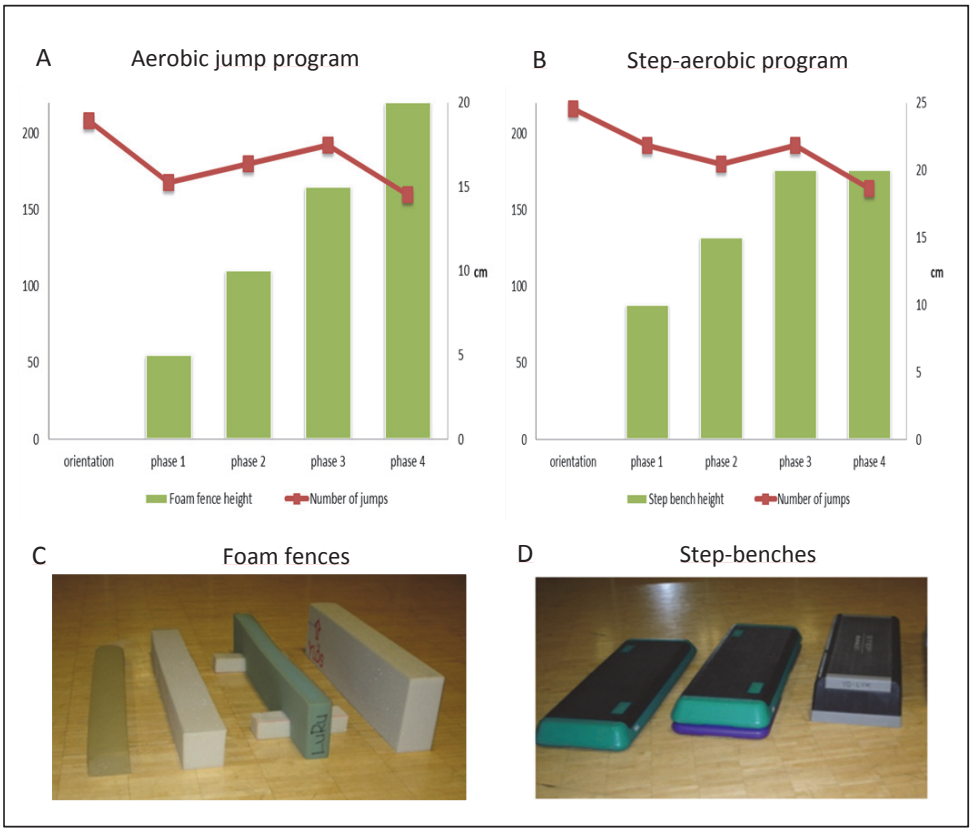


FIGURE 7 The progression of aerobic and step-aerobic exercise programs expressed as the number of jumps and height of jumping obstacles and step-benches. The green bars in the upper row represent the height of the foam fences in the aerobic program (panel A) and step-benches in the step-aerobic program (panel B). The red stacked lines show the planned number of jumps per session for each of the 3-month exercise periods.

4.4.2 Assessment of exercise loading and intensity

The high-impact exercise was quantified by recording the number and intensity of acceleration peaks (impacts) with an accelerometer-based body movement monitor (Newtest Oy, Oulu, Finland). The data on the intensity of exercise loading were collected during one exercise session in each of the 3-month training periods. The number of impacts were analyzed, as modified by Vainionpää et al. (2006) (Study III and IV), at four acceleration levels according to the multiples of acceleration of gravity, and by calculating the impact score according to Ahola et al. (2010; Study IV). To evaluate the intensity of training, mean and maximum heart rate values were collected during one exercise session in each of the 3-month exercise periods with a heartbeat monitor (Polar F6, Polar Electro Oy, Kempele, Finland). In addition, the rate of perceived

exertion (RPE) was measured after each training session on a 15-point Borg scale (Borg 1982) (Study III).

4.4.3 Adverse events

Adverse events occurring in the intervention exercise classes were counted and possible exercise-related knee pain was recorded after each training session with a visual analogue scale (VAS) (Studies III and IV). If pain severity exceeded the value 5 on a scale of 0 - 10 cm immediately after the exercise session or during the next few hours, the trainee was recommended to take a few days' break from training until the pain was alleviated. A physician was in available for possible adverse events during training.

4.4.4 Control group

Controls were encouraged to continue their lives as usual during the 12-month trial. In addition, to maintain their interest in the study, they were offered the possibility of participating in a social group meeting every third month. The social group meetings consisted mainly of lectures on healthy lifestyles and stretching exercises (not physical activity or exercise).

4.5 Statistical methods

Means with standard deviations (SD), medians with interquartile ranges (IQR), counts with percentages, or frequency distributions were used as descriptive statistics. Normality of the continuous variables was tested using the Kolmogorov-Smirnov test and Shapiro-Wilk W test. For the normally distributed variables an independent samples t-test was used to compare the means, medians and counts of the two study groups (Studies III and IV), and One-Way ANOVA was used to compare the means of more than two groups (Study II). Differences between the groups in discrete variables were analyzed with the chi-square or Fisher's exact test. In the case of violation of the assumptions (non-normality), a bootstrap-type or permutation test was used. Correlation coefficients were calculated by the Pearson method (Studies III and IV). The Epps-Singleton two-sample test for equality of distributions was used to generate the histogram of total physical activity loading for the control group and the exercise group (Study IV).

Reproducibility analyses (Study I). A coefficient of variation (CV) representing the percentage magnitude of day-to-day variability as the measure of dGEMRIC measurement reproducibility for the different knee cartilage ROIs was calculated. CV values were used to describe the variability results between the measurements for each subject, and the root-mean-square average coefficient of variation (CV_{RMS}) was used to describing the variability results for the whole group. In addition, the intra-class correlation coefficient (ICC) was

calculated to describe the error-free proportion of the variation in inter-subject scores with a 95% confidence interval (CI).

Generalized linear models (Study II). Statistical significance for the hypothesis of linearity between radiographic knee OA and bone and cartilage traits, and for the clinical factors found to be associated with radiographic knee OA, were evaluated by using generalized linear models with an appropriate distribution and link function. In addition, the strength of the associations of bone and cartilage traits with radiographic knee OA grading were tested with an effect size, which was calculated using partial Eta-squared, ($\eta 2$).

Analysis of covariance (ANCOVA, Studies III and IV). ANCOVA with 12-month measurements as dependent variables was used to assess the intervention-effect between the exercise and control groups. The group differences in the bone and physical function outcomes were adjusted for baseline values, and in addition bone mineral content was adjusted by body mass and change in body mass (Study III). In study IV, the bone and cartilage traits as outcome variables were adjusted for baseline values, age, height and body mass. Multivariate analysis of variance (MANOVA) by the bootstrap type Hotelling T-squared test was used with dGEMRIC and T2 indices in the detailed subregion cartilage analysis owing to violation of the distribution assumptions (Study III). Holm's procedure was used to adjust for multiple comparisons and to identify significant differences in at least one of the eight cartilage ROIs in the between group MANOVA comparisons. Thus 95% CIs for the MRI outcome means were obtained by bias-corrected bootstrapping. Finally, treatment effects with their 95% CIs were calculated for the treatment effect between the exercise and control groups (Studies III and IV).

Statistical power. For the RCT (Studies III and IV) the power calculations were based on the results of previous bone exercise intervention trials (Uusi-Rasi et al. 2003, Karinkanta et al. 2007) where a sample size of 70 subjects (35 in each group) was required to detect a difference of 0.08 grams (~2%) in the change in femoral neck BMC ($\alpha = 0.05$, power = 80%), taking into account a drop-out rate of approximately 10%, between the intervention group and controls. For the knee cartilage outcomes, the intended sample sizes could not be reliably calculated, as previous long-term exercise interventions for cartilage change did not exist.

All analyses in the RCT setting (Studies III and IV) were performed according to the intention-to-treat principle, meaning that the results of an experiment is based on the initial treatment assignment and not on the treatment eventually received. Compliance with the intervention (Studies III and IV) was calculated using the formula: [amount of performed exercises]:[expected number of exercises]×100. Statistical significance was set at $\alpha < 0.05$.

Statistical software. In study I analyses were performed using SPSS software version 14 (SPSS Inc, Chicago, IL, USA). In studies II and III all analyses were performed using Stata statistical software version 12.1 (StataCorp,

College Station, TX, USA). In study IV analyses were performed using SPSS software version 20.0.0.2 (IBM Corp., Armonk, NY).

5 RESULTS

5.1 Characteristics of the participants

The baseline characteristics of the participants are summarized in Table 3. The participants in the dGEMRIC reproducibility study (Study I) comprised physically active students and staff members of Faculty of Sport and Health Sciences at University of Jyväskylä, which shows as a rather high level of habitual physical activity in this group compared with the postmenopausal women (Studies II - IV). In the bone and cartilage association study no differences in age, height, weight or body mass index were observed between the postmenopausal women with mild knee OA (III and IV) and without OA (K/L 0 group; Study II). The participants with mild knee OA reported an average amount of knee pain 10 (SD 13) mm, while no knee pain (range 0 to 1 mm) was reported by the participants in the K/L 0 group. At baseline, no differences were found between the exercise group and the control group in the anthropometric measures or in physical function, knee-related symptoms or quality of life (Studies III and IV).

TABLE 3 Baseline characteristics of the participants. Values are means (SD) or n (%).

	Young adults	**Postmenopausal women**		
	Asymptomatic	**Non-OA**	**Mild knee OA**	
		K/L 0 group	Exercise group	Control group
	N = 10	N = 12	N = 40	N = 40
Age (years)	32 (6)	58 (3)	57 (4)	59 (4)
Height (cm)	174 (9)	161 (6)	164 (6)	161 (5)
Body mass (kg)	77.4 (16.4)	67.5 (10.8)	73.5 (9.5)	69.4 (11.7)
Body mass index (kg/m^2)	25.3 (3.5)	25.9 (3.7)	27.2 (3.1)	26.7 (4.2)
Kellgren-Lawrence grade, n (%)	N/A			
Grade 0		12 (100)		
Grade 1			13 (32)	13 (32)
Grade 2			27 (68)	27 (68)
Knee pain during last week (0-100 mm)		0 (0)	10 (13)	10 (13)
Habitual physical activity (MET-hour/week)	60.2 (38.5)	18.1 (12.6)	18.1 (13.0)	18.9 (17.2)
Time from menopause (years)		8.3 (5.5)	8,9 (5.9)	9.1 (5.3)
WOMAC (0-100 scale)				
Pain		2 (5)	9 (10)	6 (6)
Stiffness		5 (10)	10 (13)	9 (9)
Physical function		2 (4)	5 (6)	4 (4)
Hormone replacement therapy, n (%)		3 (25)	20 (50)	12 (30)
Pain killers in general, n (%)		7 (58)	26 (65)	17 (42)
Glucosamine use occasionally, n (%)		0 (0)	9 (23)	13 (32)
Muscle force (N)				
Knee extension[a]		381 (49)	404 (92)	414 (70)
Knee flexion[a]		172 (44)	189 (56)	178 (51)
Power (W)		1794 (286)	1954 (366)	1805 (341)
Dynamic balance[b] (s)		16.5 (1.7)	17.0 (1.5)	17.4 (2.7)
VO_{2max}[c] (mL · kg^{-1} · min^{-1})		29.4 (2.9)	28.9 (3.7)	29.2 (4.2)

TABLE 3 (continues)

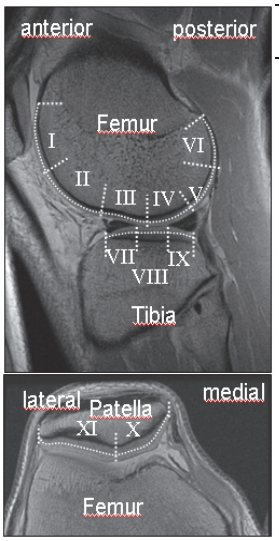
	Young adults	Postmenopausal women		
	Asymptomatic	Non-OA	Mild knee OA	
		K/L 0 group	Exercise group	Control group
	N = 10	N = 12	N = 40	N = 40
RAND-36 Item (0 - 100 scale)				
General health		77.1 (10.3)	73.5 (11.2)	73.6 (14.0)
Physical functioning		90.8 (12.0)	89.3 (9.3)	90.6 (10.3)
Emotional well-being		81.0 (12.3)	83.1 (11.4)	83.3 (12.9)
Social functioning		90.6 (12.1)	88.5 (17.5)	94.7 (11.3)
Energy		67.5 (16.9)	70.3 (15.9)	75.4 (14.2)
Pain		87.5 (16.1)	79.8 (12.6)	83.1 (14.7)
Role physical		91.7 (19.5)	89.1 (21.3)	91.3 (22.3)
Role emotional		94.4 (13.0)	84.6 (27.4)	89.2 (30.6)

WOMAC = Western Ontario and McMaster University Osteoarthritis Index, RAND-36 = health-related quality of life questionnaire.
[a]average of both legs best attempt, [b]negative number indicates better balance, [c]estimated maximal oxygen uptake.

5.2 Reproducibility of dGEMRIC measurement

Measurement reproducibility expressed as the root-mean-square average coefficient of variation (CV_{RMS}) and intra-class correlation coefficient (ICC) is given differently for superficial, deep and full-thickness ROIs in the femur, tibia and patella cartilages (Figure 8). Reproducibility expressed as the CV_{RMS} of full-thickness ROIs ranged between 4.8 and 11.6% (ICC 0.62 - 0.98) in the different cartilage segments of the femur, tibia and patella. The reproducibility of the superficial and deep cartilage ROIs ranged between 5.2 and 12.9% (ICC 0.45 - 0.93) for the femur, 5.8 and 9.3% (0.45 - 0.91) for the tibia and 4.7 and 8.3% (0.94 - 0.98) for the patella.

On average, CV_{RMS} measurement precision error was 7.4% for the superficial, 8.4% for the deep and 6.8% for the full-thickness cartilage layers covering all three cartilage sites. Reproducibility for the entire femoral, tibial and patellar cartilages were 4.2% (ICC 0.95, 95% CI 0.85 - 0.99), 5.5% (0.87, 95% CI 0.61 - 0.96) and 4.8% (0.97, 95% CI 0.90 - 0.99), respectively.



Segment	Layer*	dGEMRIC (ms)	CV_{RMS} (%)	ICC (95% CI)
Lateral femoral condyle				
I anterior aspect	s	421 (5)	6.1	0.92 (0.74-0.98)
of trochlea	d	479 (21)	9.2	0.89 (0.65-0.97)
	ft	448 (13)	6.9	0.91 (0.73-0.98)
II posterior aspect	s	385 (4)	7.1	0.93 (0.77-0.98)
of trochlea	d	448 (14)	9.9	0.91 (0.72-0.98)
	ft	413 (8)	7.8	0.92 (0.77-0.98)
III anterior central	s	448 (9)	7.0	0.86 (0.60-0.96)
femur	d	456 (4)	9.1	0.68 (0.01-0.92)
	ft	452 (4)	7.1	0.80 (0.41-0.95)
IV posterior central	s	526 (14)	5.2	0.84 (0.55-0.96)
femur	d	559 (5)	7.2	0.45 (-0.77-0.86)
	ft	541 (7)	4.8	0.81 (0.46-0.95)
V anterior part of	s	452 (13)	8.7	0.77 (0.35-0.94)
posterior femur	d	530 (19)	6.8	0.90 (0.70-0.97)
	ft	481 (11)	6.8	0.88 (0.66-0.97)
VI posterior part of	s	359 (8)	11.9	0.51 (-0.51-0.87)
posterior femur	d	405 (20)	12.9	0.67 (0.09-0.91)
	ft	379 (13)	11.6	0.62 (-0.08-0.90)
Lateral tibial condyle				
VII anterior tibia	s	420 (1)	9.3	0.88 (0.65-0.97)
	d	461 (10)	8.3	0.76 (0.32-0.94)
	ft	437 (3)	6.9	0.89 (0.68-0.97)
VIII central tibia	s	443 (7)	7.5	0.90 (0.72-0.97)
	d	524 (3)	5.8	0.75 (0.24-0.93)
	ft	478 (6)	6.0	0.88 (0.64-0.97)
IX posterior tibia	s	417 (6)	6.2	0.91 (0.74-0.98)
	d	510 (8)	7.4	0.45 (-0.70-0.85)
	ft	455 (7)	5.8	0.83 (0.51-0.95)
Patella				
X medial aspect	s	410 (11)	7.6	0.95 (0.83-0.99)
	d	499 (14)	8.3	0.94 (0.80-0.99)
	ft	449 (14)	6.1	0.96 (0.85-0.99)
XI lateral aspect	s	438 (2)	4.7	0.98 (0.94-0.99)
	d	535 (8)	7.0	0.97 (0.92-0.99)
	ft	482 (4)	5.0	0.98 (0.94-0.99)

FIGURE 8 Segmental division of femoral, tibial and patellar cartilage surfaces. Full-thickness (ft) cartilage was divided into superficial (s) and deep halves (d) as indicated by the dotted line. Nomenclature for segments I - XI and their measurement reproducibility values espressed as the root-mean-square average coefficient of variation (CV_{RMS}) and intra-class correlation coefficient (ICC) with 95% condfidence intervals (CI) are shown on the right side of the picture.

5.3 Bone and cartilage characteristics in postmenopausal women with and without knee osteoarthritis

A total of 90 postmenopausal women were categorized into three classes according to their radiographic K/L grades; 0 = normal (n = 12), 1 = doubtful (n

= 25) or 2 = minimal (n = 53). Linear regression analysis showed that in the femoral neck bone traits age-, height- and weight-adjusted bone mineral content (BMC) (p for linearity = 0.019), section modulus (Z) (p for linearity = 0.033) and cross-sectional area (CSA) (p for linearity = 0.019) was significantly higher with higher OA grades (Table 4).

TABLE 4 Femoral neck bone traits and knee cartilage traits (mean, standard deviation) according to radiographic Kellgren-Lawrence (K/L) grades.

Variable	K/L 0 (n = 12)	K/L 1 (n = 25)	K/L 2 (n = 53)	P for linearity
BONE TRAIT				
Bone mineral content (BMC), g	4.18 (0.84)	4.46 (0.87)	4.73 (0.58)	0.019[a]
Section modulus (Z), mm^3	543 (98)	611 (170)	628 (101)	0.033[a]
Cross sectional area (CSA), mm^2	135 (22)	142 (28)	150 (19)	0.019[a]
T2, ms				
Medial condyle				
Posterior part of central femur	50.4 (2.8)	49.6 (6.3)	50.2 (5.4)	0.85[a]
Central tibia	44.2 (5.2)	44.9 (4.8)	45.1 (4.2)	0.60[a]
Lateral condyle				
Posterior part of central femur	50.8 (5.4)	50.5 (6.0)	50.4 (5.6)	0.83[a]
Central tibia	38.4 (2.4)	43.5 (6.5)	42.0 (7.3)	0.20[a]
dGEMRIC index, ms				
Medial condyle				
Posterior part of central femur	446 (60)	461 (55)	456 (78)	0.79[b]
Central tibia	362 (67)	412 (72)	402 (58)	0.17[b]
Lateral condyle				
Posterior part of central femur	474 (67)	512 (75)	469 (59)	0.28[b]
Central tibia	426 (107)	433 (82)	437 (77)	0.63[b]

[a]Adjusted for age, body mass, and height.
[b]Adjusted for age.

The effect sizes indicated that the linear association was moderate, i.e., in BMC, η^2 was 0.08, in Z 0.04 and in CSA 0.05. Mean ratios (K/L grades 1 - 2 versus K/L 0) are given in Figure 9. BMC was 1.10 times higher in grade K/L 2 than K/L 0 grade. Z was 1.12 times higher in grade K/L 2 than K/L 0. CSA was 1.08 times higher in grade K/L 2 than K/L 0. The ratios did not differ between grades K/L 1 and K/L 0 (Figure 9).

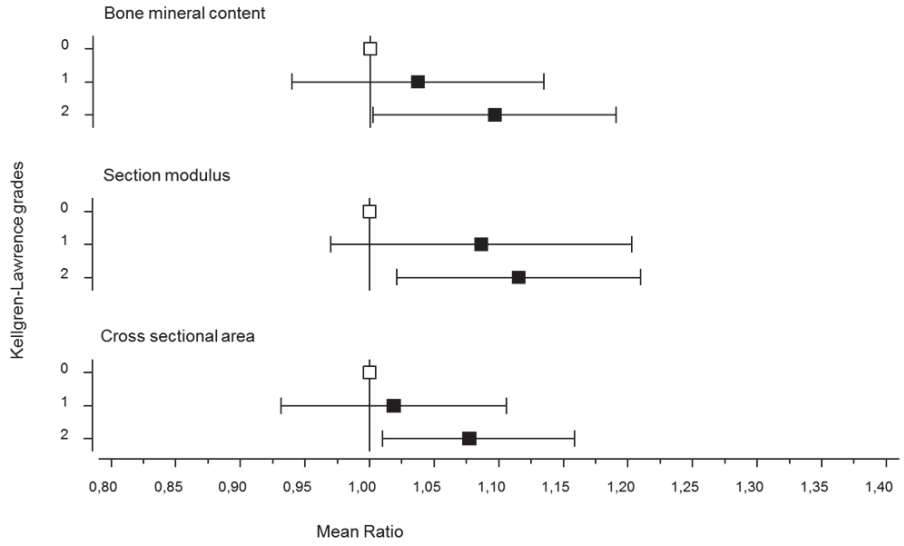


FIGURE 9 Age-, height- and weight-adjusted bone trait mean ratios with 95% confidence intervals for Kellgren-Lawrence grades 1 and 2 in relation to Kellgren-Lawrence grade 0.

In knee-related symptoms, a linear relationship was observed between OA grade and symptoms, showing that the higher the OA grade, the greater the knee pain ($p = 0.008$ for linearity), stiffness ($p = 0.036$), and physical disability ($p = 0.033$) reported by the subjects. In contrast, no linear relationship was found between the OA grades and knee cartilage T2 or dGEMRIC indices (Table 4) or physical function measures.

5.4 Effects of high-impact training in postmenopausal women with mild knee OA

During the 12-month intervention, mean daily physical activity outside of the intervention sessions, expressed as DIS_{Log}, did not differ between the exercise group 163 (SD 43) and the control group 168 (46) ($P = 0.64$). Instead, the total physical activity loading index, given as DIS_{Total}, was significantly higher in the exercise group (364 [SD 73]) than in the control group (168 [46], $P < 0.01$), indicating that the group difference in impact was due to the exercise program. The percentage distribution of mean DIS_{Total} for the exercise group and the control group is shown in Figure 10. Throughout the study period, mean habitual physical activity was 32.1 (SD 12.6) MET-hours/week (intervention exercise classes not included) in the exercise group, as compared to 23.1 (15.9) MET-hours/week ($P = 0.01$) in the control group.

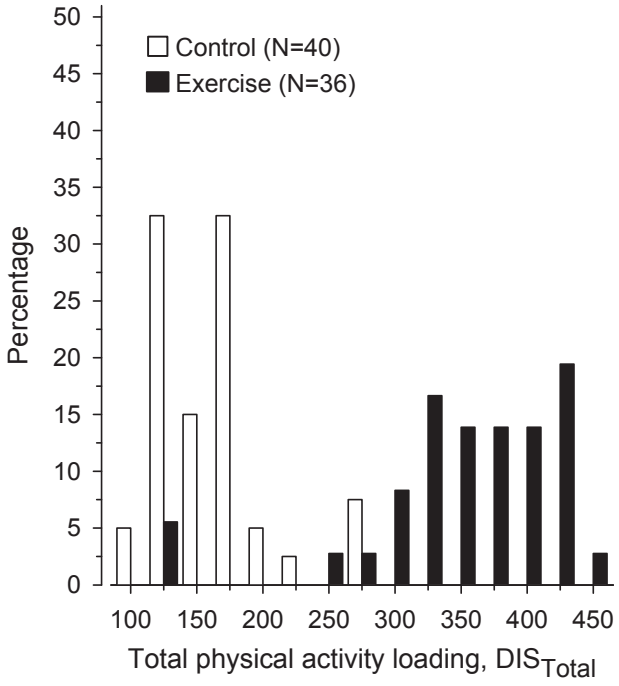


FIGURE 10 Percentage distribution of the total physical activity loading index (DIS_{Total}) for the control group and the exercise group over the 12-month study period. In the controls, DIS_{Total} is same as the average daily impact score (DIS_{Log}) while in the exercisers it includes DIS_{Log} and the average impact loading of the exercise intervention.

5.4.1 Feasibility of the high-impact exercise intervention

Drop-outs. Only four persons (5%) from the exercise group withdrew from the study. Two participants withdrew immediately after randomization and two others discontinued their participation at weeks 3 and 5. These participants were not reached after several phone call and e-mail attempts. *Adherence.* With lost trainees included, attendance at all the training sessions offered was 68% (range 0 to 100%), and the mean training frequency was 2.1 (SD 0.9) times per week. Attendance excluding the lost trainees was 72% (range 8 to 100%) and the mean training frequency 2.2 (SD 0.8). *Adverse events*. Six trainees (17%) consulted the attending physician due to musculoskeletal injuries or other symptoms during the 12-month intervention. In all of these cases, treatment was a break from training. All six trainees returned to the exercise regimen within 5 to 21 days. Mean exercise-related knee pain measured in all trainees after each training session was 5 mm (range 0 - 82 mm). In the control group, two visits were made to the attending physician due to previous meniscal tear injury and cardiac dysrhythmia. The number of visits to the attending physician did not differ significantly between the groups ($p = 0.15$).

Exercise loading intensity. The mean number of acceleration peaks per training class was 2275 (SD 343). For more details, see original studies III and IV. The mean exercise-induced exertion rate was 14 (between "somewhat hard" and "hard") on a scale 6 to 20, and mean and maximum heart rate values were 111 and 148 beats $\cdot min^{-1}$, respectively.

5.4.2 Effects on physical function

Dynamic balance in figure-of-eight running ($p < 0.01$) improved by 3% in the exercise group compared to controls (Figure 11). The exercise group also showed an increase of 11% in isometric knee extension force ($p < 0.01$) compared to the control group (Figure 11). Additionally, aerobic fitness ($p = 0.03$) improved by 4% in the exercise group compared to the control group (Figure 11). No between-group differences in isometric knee flexion force ($p = 0.45$) and leg extension power ($p = 0.22$) were observed after the intervention.

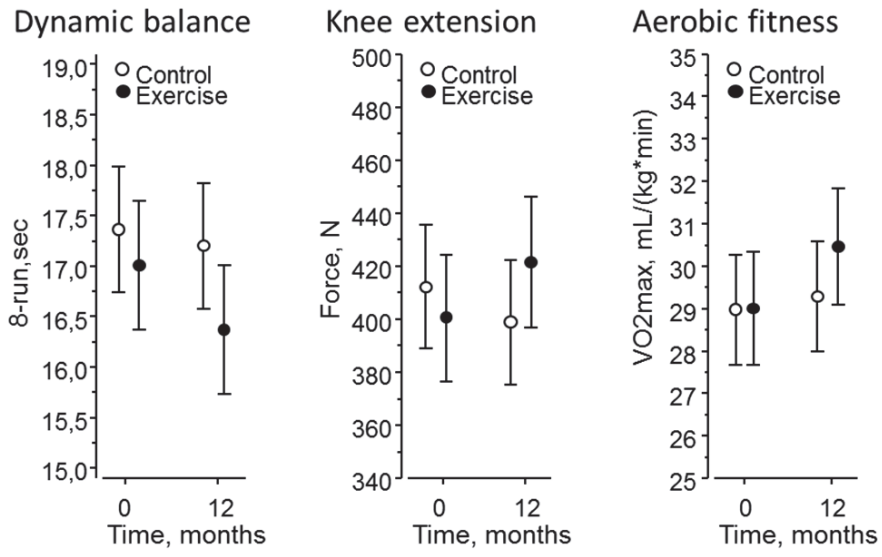


FIGURE 11 Mean changes (95% confidence intervals) in physical function measures of dynamic balance (left), knee extension force (middle), and aerobic fitness (right).

5.4.3 Effects on clinically important symptoms

The scores for pain (ANCOVA, baseline as covariate, p = 0.47), stiffness (p = 0.29) and physical functional difficulty (p = 0.12) were not affected by the exercise program (Figure 12).

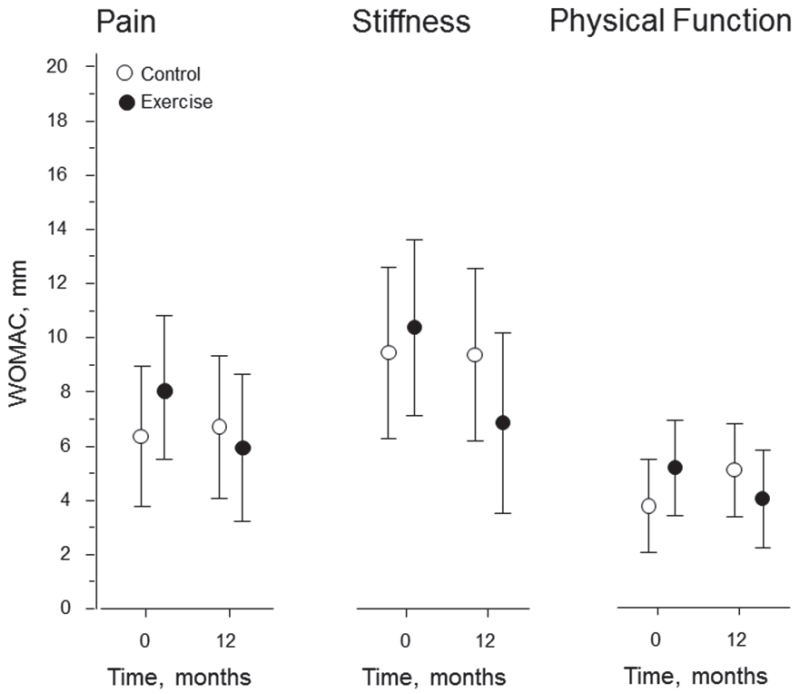


FIGURE 12 Mean changes (95% confidence intervals) of WOMAC subscales of pain (left), stiffness (middle), and physical function (right).

5.4.4 Effects on bone mass and structure

Absolute values for bone mass and bone structural properties at baseline, change in these at 12-months, and treatment effects are given in Table 5.

After the 12-month trial, the exercise group had gained 0.6% whereas the control group had lost 1.2% in femoral neck BMC (Figure 13 A). The training effect was significant (p < 0.001). The training also improved femoral neck Z by 3.1%, while in the control group it decreased by 1.4%. The training effect in Z was significant (p = 0.007). No relationship was found between femoral neck BMC change and training compliance (Figure 13 B).

TABLE 5 Baseline, change and treatment values of bone mineral content (BMC) in femur and lumbar spine, and femoral neck bone structural traits obtained by advanced hip structure analysis (AHA).

	Baseline, Mean (SD)		Change to Month 12, Mean (95% CI)		Treatment effect	P-value	
	Exercise	Control	Exercise	Control	Mean (95% CI)	Crude	Adjusted[a]
BMC [g]							
FN	4.80 (0.76)	4.50 (0.62)	0.03 (-0.01 to 0.07)	-0.06 (-0.10 to -0.02)	0.09 (0.03 to 0.14)	0.002	<0.001
TROC	11.40 (2.19)	11.57 (2.33)	0.12 (-0.07 to 0.30)	-0.01 (-0.20 to 0.17)	0.13 (-0.12 to 0.39)	0.31	0.41
L2 - L4	53.00 (9.04)	51.81 (9.23)	0.26 (-0.50 to 1.02)	-0.63 (-1.21 to -0.05)	0.90 (-0.04 to 1.82)	0.060	0.086
AHA							
Z [mm]	640 (146)	609 (109)	18 (-3 to 34)	-9 (-20 to 2)	28 (10 to 47)	0.003	0.007
CSA [mm^2]	153 (24)	143 (20)	0 (-2 to 2)	-2 (-3 to 0)	2 (-0 to 5)	0.078	0.093
W [mm]	49.2 (4.2)	48.9 (4.8)	-0.5 (-1.1 to 0.2)	-0.1 (-0.9 to 0.7)	-0.3 (-1.2 to 0.6)	0.50	0.57

SD = standard deviation, CI = confidence interval, FN = femoral neck, TROC = trochanter, L2 - L4 = lumbar spine vertebrae L2 - L4, Z = section modulus, CSA = cross-sectional area, W = width.
[a]adjusted by baseline values and body mass.

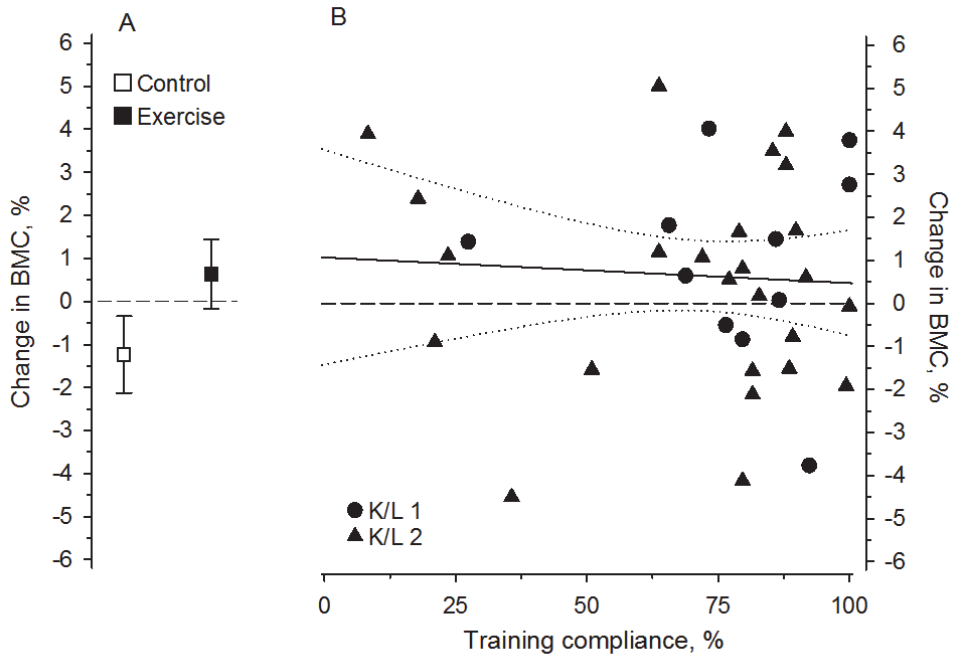


FIGURE 13 Percent change with 95% confidence intervals in femoral neck bone mineral content (BMC) in the exercise and the control groups (A), and the relationship between training compliance and the change in BMC in the exercise group according to Kellgren and Lawrence (K/L) radiographic grade (B).

5.4.5 Effects on cartilage indices

The treatment effects for ROIs are given differently for the bulk cartilage areas exposed to exercise loading in the medial and lateral femoral condyles (Figure 14 A, Study IV) and for detailed subregions in the medial and lateral condyles in the femur and tibia (Figure 14 B, Study III). The baseline and follow-up values and the treatment effects for the bulk dGEMRIC indices and T2s are presented in Table 6. The baseline values, changes in these at 12-months and the treatment effects for detailed subregions are presented in original study III.

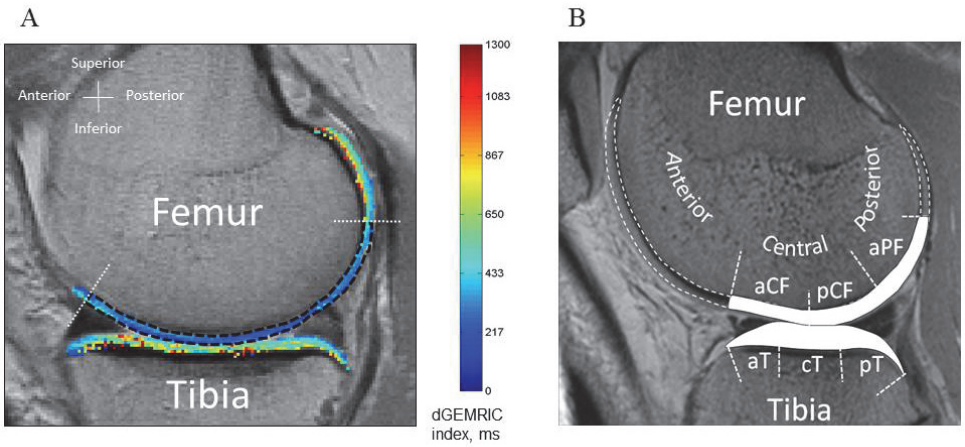


FIGURE 14 Knee cartilage regions-of-interest (ROIs) used in Study IV (A) and Study III (B). In Figure A, a bulk cartilage ROI at the femur is outlined by the dashed lines. In Figure B subregional ROIs at the femur and tibia are marked in white color. Nomenclature for abbreviated subregions in Figure 14 B: aCF = anterior central femur, pCF = posterior central femur, aPF = anterior part of posterior femur, aT = anterior tibia, cT = central tibia, pT = posterior tibia. Figure A illustrates a single sagittal slice from the center of the medial femoral condyle and B from the center of the lateral femoral condyle.

TABLE 6 Baseline, follow-up, and treatment values of dGEMRIC index and T2 from the bulk femoral cartilages.

Quantitative MRI	Baseline, Mean (SD)		Follow-up Mean (SD)		Treatment effect		P-value	
	Exercise (n=36)	Control (n=40)	Exercise (n=36)	Control (n=40)	Crude mean (95% CI)	Adjusted mean (95% CI)	Crude	Adjusted
dGEMRIC [ms]								
Medial	453 (54)	469 (53)	457 (67)	459 (64)	10 (-15 to 36)	10 (-15 to 36)[a]	0.47	0.45[a]
Lateral	458 (57)	466 (46)	460 (44)	468 (52)	-5 (-24 to 15)	-8 (-26 to 12)[a]	0.61	0.44[a]
T2 [ms]								
Medial	51.2 (3.7)	50.0 (4.6)	51.5 (5.2)	49.4 (3.9)	1.1 (-0.3 to 2.5)	1.3 (-0.1 to 2.7)[b]	0.12	0.088[b]
Lateral	49.4 (4.2)	49.9 (3.5)	50.0 (5.1)	50.4 (3.6)	-0.4 (-2.5 to 1.6)	-0.6 (-2.6 to 1.3)[b]	0.69	0.54[b]

SD = standard deviation, CI = confidence interval.
[a]Adjusted by baseline value and age.
[b]Adjusted by baseline value, age, height and body mass.

In the bulk cartilage ROIs, after the 12-month trial, no between-group differences were observed either in the medial or lateral condyle or with the T2 or dGEMRIC mapping techniques. Similarly, in the detailed analysis of the cartilage subregions, after corrected multiple comparisons, no between-group differences were found in any of the dGEMRIC indices or T2s (Figure 15).

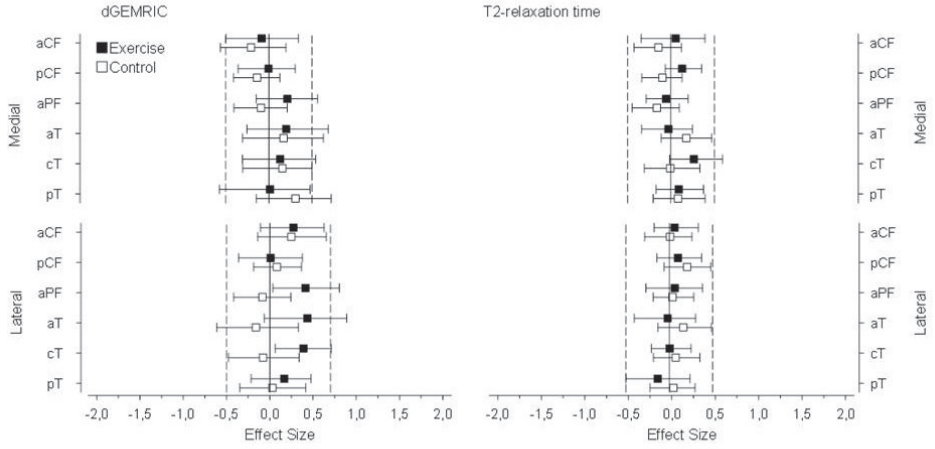


FIGURE 15 Effect sizes at different cartilage subregions with both dGEMRIC and T2 relaxation time techniques. Medium (0.50) effect sizes are illustrated with dotted lines. Nomenclature for abbreviated segments: aCF = anterior central femur, pCF = posterior central femur, aPF = anterior part of posterior femur, aT = anterior tibia, cT = central tibia, pT = posterior tibia.

5.4.6 Relationship between changes in bone and cartilage

No relationships were observed between changes in femoral neck BMC and changes in the knee cartilage dGEMRIC indices in the medial or lateral condyles of the posterior central femur, or in the medial or lateral condyles of the central tibial cartilage. However, there was an association between change in femoral neck Z and change in bulk cartilage T2 at the medial femoral condyle, showing that Z increased with decreasing T2 relaxation time (Figure 16 A). In addition, there was an association between change in the bulk cartilage dGEMRIC index at the lateral femoral condyle and change in femoral neck Z, showing that Z increased with a higher dGEMRIC index (Figure 16 D).

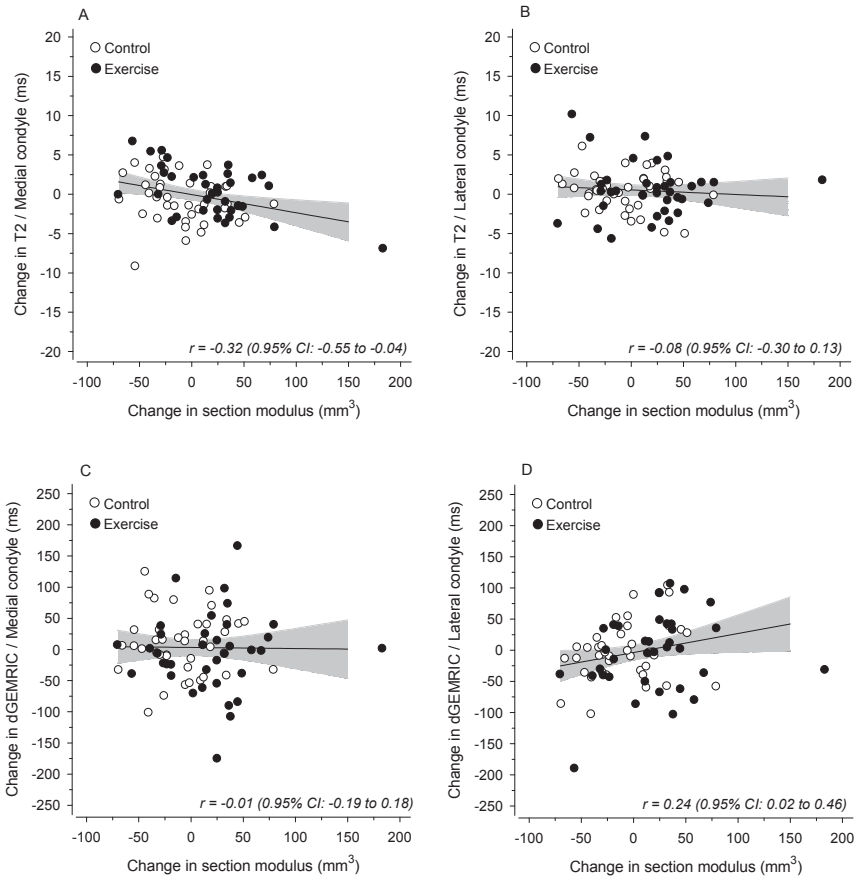


FIGURE 16 Associations between change in the femoral neck section modulus and change in T2 (upper row) and dGEMRIC indices (lower row) for bulk femoral cartilage.

6 DISCUSSION

The aim of this study was to investigate whether the dGEMRIC cartilage imaging method is reproducible and could be therefore used as a reliable instrument for monitoring possible exercise-induced changes in cartilage. In addition, the associations between the severity of radiographic knee OA and femoral neck bone mass and strength were investigated in a cross-sectional study in postmenopausal women. Finally, the effects of a progressive high-impact exercise program on bone and articular cartilage properties was studied in postmenopausal women with mild knee OA.

The dGEMRIC reproducibility study demonstrated good day-to-day measurement accuracy, thereby showing it to be feasible method for application in the subsequent training intervention study. The cross-sectional study showed that femoral neck bone mineral mass and strength increased as the knee OA became radiographically more severe. These results have implications for the hypothesis that there is an inverse relationship between OA and OP. Twelve months of progressive high-impact exercise increased femoral neck BMC and strength, and also improved physical performance–related risk factors for falls, such as muscle strength and dynamic balance. The training had no harmful effects on tibiofemoral cartilage, indicating that cartilage has the ability to maintain its biochemical composition under intensive loading. The results of the present RCT suggest that when progressively implemented, high-impact exercise is feasible in the prevention of OP and physical performance–related risk factors for falling in postmenopausal women with mild knee OA.

6.1 The reproducibility of the cartilage MR imaging methods used in this thesis

Two methods specifically designed to image cartilage biochemical composition, dGEMRIC and T2 relaxation time, were used as tools for assessing the change in cartilage in this longitudinal study. Given that the measurement consistency

is prerequisite for reliable cartilage imaging and that this matter had not previously been systematically studied, verifying the reproducibility of the dGEMRIC and T2 imaging methods were the first priority before the exercise intervention could be initiated. In addition of dGEMRIC reproducibility experiment conducted here, Hannila et al. (2009) reported mostly good T2 mapping reproducibility (CV ~5%) among healthy adult for knee cartilage in the femoral, tibial and patellar compartments.

Our dGEMRIC reproducibility results, with means of 5% for bulk ROIs, 7% for full-thickness ROIs, 7% for superficial ROIs and 8% for deep ROIs, showed good measurement accuracy in light of the fact that a CV% lower or equal to 10% is acknowledged to be an indicator of good measurement reliability (Atkinson & Nevill 1998). The key factors affecting reproducibility were related both to joint-related factors, such as the positioning of the joint and timing of the contrast agent injection, and imaging-related factors, such as slice positioning, accuracy of segmentation and partial volume effect.

More recently two other studies systematically investigating the reproducibility of dGEMRIC have been published (Siversson et al. 2010, van Tiel et al. 2013). Siversson and colleagues (2010) investigated the reproducibility of dGEMRIC with respect to different acquisition techniques in nine patients with an anterior cruciate ligament tear. Their repeatability results with the two-dimensional (2D) inversion recovery and three-dimensional (3D) Look-Locker techniques were of same magnitude as our results with the 2D technique in healthy subjects. In another study, van Tiel and colleagues (2013) investigated the reproducibility of high-field strength (3 Tesla), high-resolution 3D dGEMRIC in 20 patients with early stage knee OA. They also reported good measurement reproducibility, with ICCs ranging from 0.87 to 0.95, depending on the anatomical position of the ROI. The authors concluded that dGEMRIC can be used to evaluate cartilage quality changes in longitudinal research in patients with early stage OA (van Tiel et al. 2013). On the other hand, it has to be acknowledged that if cartilage responses in future exercise studies are of the same order of magnitude as those in our training intervention, then the measurement error of the dGEMRIC technique casts a shadow over its prospects as an evaluation tool.

6.2 Associations between radiographically-assessed knee OA and femoral neck bone structural characteristics in postmenopausal women with and without mild knee osteoarthritis

We examined the associations between radiographic knee OA and femoral neck bone structure, strength and mineral mass in postmenopausal women with and without mild knee OA. The results showed that a linear association between femoral neck bone characteristics and radiographic grades from K/L 0 to 2, so

that the worse the knee OA, the higher the femoral neck bone mineral mass and strength. This finding is in line with the large cross-sectional study cohorts, mostly conducted among middle-aged and elderly women, indicating that knee OA is associated with increased femoral neck bone mineral mass or density (Hannan et al. 1993, Hart et al. 1994, Burger et al. 1996). The mechanism whereby OA subjects have denser and stronger bones than non-OA subjects remains unknown, but the hypothesis for this association include the explanation that higher bone mineral mass increases subchondral bone stiffness, and therefore joint loading and the risk for joint OA (Sudo et al. 2008, Burr & Gallant 2012).

The results of this study also support the hypothesis of an inverse relationship between OA and OP despite the fact that our study did not include subjects with progression to severe knee OA (K/L grades 3 and 4) or OP, as we used baseline data from the exercise intervention and its exclusion criteria (Studies III and IV). Although it is commonly held that there is an inverse relationship between OP and OA, some experimental data have also shown the opposite (Calvo et al. 2007). It has also been noticed that the bone site measured has an influence on the relationship between bone density and knee OA. In the large Framingham Study cohort, appendicular skeleton BMD (radius) was not associated with knee OA, whereas proximal femur BMD was associated with knee OA (Hannan et al. 1993). In addition, while most cross-sectional studies have reported an inverse relationship between OA and OP, some longitudinal studies have reported a more complicated relationship. In those studies older subjects with radiographic OA have exhibited a higher rate of bone loss than subjects without OA (Hochberg et al. 2004, Ding et al. 2010). Furthermore, no definite relationship has been found when knee OA has been defined as a 2-dimensional joint space narrowing procedure (Hannan et al. 1993, Hart et al. 1994). In contrast, femoral BMD has been found to be higher in women whose knee OA has been defined by osteophytes and K/L grading according to a 3-dimensional procedure (Burger et al. 1996). These various findings show that the relationship between OA and OP is complicated, and may differ by disease site, stage or how radiographic knee OA is defined.

In the present study, the association between radiographic knee OA and the biochemical composition of cartilage was examined in a secondary analysis. No linear relationship was found between the severity of radiographic knee OA and quantitative MRI measures of T2 or the dGEMRIC index at any knee joint site. Parallel results have recently been reported in a study where T1, T2 and dGEMRIC were not linearly related to arthroscopic grading in patients with knee pain (Casula et al. 2014). The authors considered that loss of cartilage and the quality of the remaining cartilage may not be directly associated (Casula et al. 2014). A possible explanation for our finding is that while radiography measures the degree of osteophyte formation, quantitative MRI assesses cartilage quality by evaluating its biochemical composition. Thus, an association is not necessarily to be expected. Secondly, the compositional changes in cartilage in early OA most likely precede changes in the subchondral

bone and cartilage quantity. Finally, there are anomalous findings on changes in cartilage content in early OA. For example, a recent dGEMRIC study suggested that dGEMRIC-derived sulphated glycosaminoglycan (sGAG) content may remain at rather constant levels in early hip OA due to self-repair of the articular cartilage by compensative sGAG synthesis prior to gross degeneration (Stubendorff et al. 2012). In fact, a slight non-significant increase in the dGEMRIC indices in the K/L grade 1 group compared to K/L grade 0 group was also noticed in our study. Although our results for the K/L grade 0 group are based on a rather small sample size, they may indicate the occurrence of a more complex pattern of GAG content behaviour in the early stage of OA than hitherto thought. Due this non-linear behaviour of GAG content, there was also no association between the dGEMRIC indices and femoral neck bone content. Nevertheless, the qMRI results of this study challenge the value of radiographic evaluation of OA in the early stages of the disease, since the articular cartilage has an important role in OA development that is not adequately addressed using K/L scoring.

Our study also demonstrated that symptoms, especially knee pain, were strongly linearly associated with OA across K/L grades from 0 to 2, despite published results on the poor correlation between radiographic changes and clinical symptoms (Creamer & Hochberg 1997, Hannan et al. 2000). Improved MRI techniques have raised expectations regarding the ability to reveal the cause of knee pain at an early stage of OA by visualizing the non-bony sources of pain. In a recent MRI study, the prevalence of knee cartilage lesions was significantly associated with knee pain status in subjects without radiographic OA, but with risk factors for OA (Baum et al. 2012). Knee pain has also been found to be associated with elevated cartilage T2 values (Dunn et al. 2004, Baum et al. 2012), although the hyaline cartilage itself cannot generate pain because of the lack of nociceptors. There is also some evidence, obtained using standard MRI techniques, for an inverse relationship between pain and cartilage volume (Hunter et al. 2003, Wluka et al. 2004). However, the origin of pain in knee OA is still poorly understood, and according to Felson (2005) the stimuli causing pain are related to, but fundamentally different from, those producing cartilage losses (Felson 2005).

6.3 Exercise intervention

The most efficient exercise modality to improve bone strength is a combination of moderate to high-impact weight-bearing activities that are variable in nature (i.e., multidirectional) and applied rapidly (Daly 2007). Such exercise interventions have been conducted with favourable bone results in healthy subjects, including children, and premenopausal, postmenopausal and elderly women. Previously, in subjects with OA this type of exercise was thought to be harmful for the integrity of the articular cartilage, although the issue had never been scientifically tested. In our current RCT study, we carried out a 12-month

progressive high-impact-type multidirectional modified aerobic and step-aerobic jumping exercise program in postmenopausal women with mild knee OA. The first priority from the participants' point of view was the safety and suitability of this kind of intensive weight-bearing exercise regimen, since similar training programs for OA subjects had not been implemented before. Based on knowledge from the manifold pain follow-ups during the intervention, the training was well tolerated; it did not induce knee pain nor did it increase knee stiffness. During the 12-month exercise intervention, only six trainees consulted the study physician due to musculoskeletal injuries or other symptoms. All the symptoms were minor, and all trainees were able to return to their exercise without further symptoms. The average perceived exertion of exercise for the whole study period was between "somewhat hard" and "hard" (RPE value 14), although the average heart rate value remained relatively low (111 beats×min^{-1}) and the training was intended to be aerobic. As perceived exertion ranging from 6 to 20 on the Borg's RPE scale is conventionally denoted as heart rates ranging from 60 - 200 beats*min^{-1} (Borg 1982), this uneven relationship in our study may be partly caused by the fact that four trainees (11%) were using beta blockers as a treatment for high blood-pressure. Nonetheless, as a whole, the progressive high-impact exercise program was both safe and suitable, as the trainees were able to perform a long-lasting exercise program with rather high training compliance (68%) and a small drop-out rate (5%).

After the 12-month trial, we found an osteogenic effect on femoral neck bone mass and bending strength. Our results on femoral neck bone mass are in line, at least in part, with a meta-analysis reporting that, when combined with resistance training, mixed-impact loading programs, including low- to moderate-impact exercises such as jogging with walking and stair climbing, were the most effective for preserving femoral neck and lumbar spine bone mineral mass or density in postmenopausal women (Martyn-St James & Carroll 2009). Interestingly, more strenuous high-impact only and odd-impact only protocols were ineffective in increasing bone mineral mass. In contrast, to the results of this meta-analysis by Martyn St-James & Carroll (2009) showing a positive response to exercise at the lumbar spine, we did not find any effect of high-impact exercise on bone mineral mass at this site. The somewhat different group characteristics, exercise protocols, and exercise adherence between the studies may at least partly explain the inconsistent results. With regard to femoral neck bone strength, our study showed that high-impact training can positively modify femoral neck bending strength in postmenopausal women. This disagrees with prior RCT studies in early postmenopausal women (Uusi-Rasi et al. 2003), older postmenopausal women (Karinkanta et al. 2007) and breast cancer pre- and postmenopausal women (Nikander et al. 2012) that have not found exercise-induced improvements in femoral neck strength. Thus, in our study, bones were more responsive to impact exercise loading, although some improvements, more distally in the tibia, in pQCT-derived bone mass and geometry have been found following weight-bearing jumping exercises in

postmenopausal women (Hamilton et al. 2010). Nonetheless, our finding that femoral neck bone mass and strength can be improved by increased physical activity points to the importance of high-impact loading on bone structure and competence among postmenopausal women. This piece of information is of great clinical importance in fracture prevention, as the femoral neck site is widely recognised to be related to substantial osteoporotic fracture (Cummings et al. 1993, Metcalfe 2008).

The novelty of this study is that for the first time the effects of exercise were examined directly at the level of the articular cartilage in subjects with knee OA in addition to the more commonly used clinical outcomes of pain and function. Although pain scores and function are important clinical measures, they cannot provide information on whether the articular cartilage, the key factor in early pathological changes in OA, can adapt to mechanical stimuli by altering its biochemical composition, as assessed by qMRI measures, the dGEMRIC index and T2. Based on the previous exercise intervention studies in patients at risk for knee OA (Roos & Dahlberg 2005) and a follow-up study of asymptomatic female runners (Van Ginckel et al. 2010), it might have been expected that increased physical activity would positively affect the biochemical composition of cartilage. However, our study revealed that progressively implemented high-impact loading did not have effects on cartilage content at the medial or lateral tibiofemoral compartments. These disparities in cartilage results between previous exercise trials (Roos & Dahlberg 2005, Van Ginckel et al. 2010) and ours may at least partly be explained by the age of the participants and the pathophysiological condition of their knee cartilage. The older participants with the more degraded knee cartilage in our study may have a more limited ability for change in cartilage biochemical composition after increased physical activity than younger and healthier subjects. After all, with aging the capacity of the chondrocytes to synthesize some types of proteoglycans, their proliferative capacity, and their response to anabolic stimuli, including growth factors, decreases (Buckwalter et al. 2005). Also, high-impact exercise may not provide the optimal loading modality for patients with knee OA.

In the present study, rather high peak tibiofemoral compressive forces of over 3.9 g (which corresponds to 4.9 times body mass) were applied on average almost 100 times per training class. This suggests that although knee cartilage in mild knee OA may not have the full adaptation capacity needed to undergo positive biochemical structural changes in response to high-impact loading, it nevertheless has the ability to withstand physiologic compressive, tensile, and shear forces on the regions that are most highly exposed to weight-bearing loading, and therefore the most clinically relevant zones with regard to OA. Thus, even rather intensive exercise, if progressively implemented, is safe for cartilage health in mild knee OA. This finding is in line with the result of the recent meta-analysis of Henriksen et al. (2014) showing no causality between knee joint loading and the structural progression of knee OA (Henriksen et al. 2014). Furthermore, in our secondary analysis in the patellofemoral joint, the

results showed significant benefits of exercise for patellar cartilage T2 values (Koli et al. 2015). In particular, in the deep half of the tissue and in the lateral segment of patella, the T2 values were 8 - 10% in favor of the exercise group, suggesting improved cartilage quality. It remains uncertain why the results for the patellofemoral joint differ from those for the tibiofemoral joint, but different biomechanical forces in mechanical loading (Taylor et al. 1998) may explain, at least in part, the positive loading adaptation of the patellofemoral joint.

In clinically important symptoms, no statistically significant differences in the WOMAC subscales of pain, stiffness and physical function were observed between the groups following the intervention. One possible explanation for this is that since the present participants had only mild symptoms when they entered the study, the WOMAC outcome measures may not have been sensitive enough to capture subtle changes in these symptoms at the population level. For instance, there was a slight decrease in pain in the exercise group (-2 mm, 95% CI; -6 to 3 mm) although of almost no clinical relevance, since a minimum absolute change of -20 mm on the 0 – 100 mm VAS is needed to detect a minimal clinically important improvement in pain in knee OA patients (Tubach et al. 2005). Moreover, when WOMAC is used as an outcome measure, the point in time at which the subject reports pain may reflect a "good" or "bad" day, despite the fact that the items on the intensity of symptoms in WOMAC pertain to a longer time period, i.e., the past week. Due to the aforementioned low baseline values and wide day-to-day variation in pain, it is possible that some participants reached the floor levels afforded by the measure. It is difficult, therefore, to make a precise interpretation of the effects on pain of the 12-month training period. Nonetheless, the results of the WOMAC subscales used in this study provided meaningful information by showing a trend in favour of the exercise group and indicating the viability of a high-impact training program. Future evaluations may need to incorporate questionnaire subscales that measure arthritis-related symptoms at a very early stage of knee OA.

The physical performance-related risk factors for falls measured in this study were dynamic balance, maximal isometric knee extension and flexion forces, leg extension power and aerobic fitness. Of these, high-impact training had significant favourable effects on dynamic balance, knee extension force and aerobic fitness. This concurs with previous exercise trials which have found physical performance improvements after a 12-month weight-bearing multi-component exercise regimen in postmenopausal and elderly women (Welsh & Rutherford 1996, Bassey et al. 1998, Uusi-Rasi et al. 2003, Karinkanta et al. 2007, Uusi-Rasi et al. 2015). Knee extension force in particular improved significantly more (11%) in the exercise group than in the control group in our study. This is reasonable, as the knee extensor muscles were actively engaged during the weight-bearing training sessions, causing versatile and rapid body movements, and, through negative work, attenuating high-impact forces. The training of muscle force is important in elderly subjects, as good muscle force has a protective role against radiographic knee OA in women (Slemenda et al. 1998) as well as falls and fracture prevention (Karinkanta et al. 2010). Aerobic fitness

also improved significantly more (4%) in the exercise group than control group in this study. This change can be expected after three 60-minute training session per week. In addition, the habitual physical activity data gathered at baseline showed that all the participants had a rather sedentary lifestyle, implying deconditioning, which is quite common in OA subjects (Philbin et al. 1995). Thus, improvement in cardio-respiratory reserve-capacity is relatively easy when physical condition is initially low. However, somewhat surprisingly, the high-impact exercise, incorporating components requiring leg strength and power, did not elicit improvements in leg extension power as measured with the counter movement jump or knee flexion force. Leg extension power also improved in the control group implying the possibility of increased physical activity, as was in fact confirmed by inspection of the amounts of habitual physical activity as MET-hours/week at baseline and during the study. In addition, estimating the explosive characteristics of the lower limb by the counter movement jump turned out to be a complex test for some participants to perform, and if special care was not taken to ensure correct performance of the test, the results for those who had difficulty could be somewhat misleading. However, on the whole these results speak favourably for physical performance, and indicate the suitability of a high-impact exercise program as a fall prevention strategy.

6.4 Methodological consideration

This study is based on a randomized controlled trial with the primary aim of investigating the effects of high-impact training on BMC and estimated biochemical composition of cartilage in postmenopausal women with mild knee OA. In addition, a methodological study on the reproducibility of the dGEMRIC measurement and a cross-sectional study examining the association between radiographic knee OA severity and femoral neck bone and knee cartilage traits in postmenopausal women were conducted. In all studies, the estimated biochemical composition of cartilage was measured using the same dGEMRIC and T2 mapping techniques and according the same measurement protocols. In addition, the participants for the cross-sectional study, consisting of women with mild knee OA and age-matched non-OA women were selected using the same eligibility criteria and by applying the same measurement protocol. Thus the results from the different studies forming this thesis complement each other. However, the strict inclusion and exclusion criteria for the RCT somewhat weaken the generalizability of the results of the cross-sectional study. Similarly, the results of the training intervention apply to normal or somewhat overweight postmenopausal women with mild knee OA only, and cannot be generalized to adolescents, premenopausal women, postmenopausal women over 65-years of age, men or those who have more progressed knee OA.

The bone outcome measure used in this study was bone mineral content (BMC) rather than bone mineral density (BMD or areal BMD) which is more often used in the bone literature. Our reason for favoring BMC over a BMD was based on the fact that, in the physical sense, BMC is a more direct measure of bone structure and competence than aBMD as it denotes the amount of building material in a given bone structure, whereas aBMD is basically a trait that lumps together all the bone structural traits. Also, BMC reflects changes in bone mineral content, and thus is a reasonable indicator of bone mineral status, especially in prospective studies (Sievänen 2000).

Study limitations and strengths

In the cross-sectional study on bone and cartilage indices in radiographic knee OA, owing to the RCT-related exclusion and inclusion criteria, we had a rather small and selected sample, which resulted in uneven distributions in all the comparisons between different K/L grade groups. However, the effect sizes (partial Eta-squared, $\eta 2$) indicated that for the bone traits the linear association was at a moderate level, suggesting that a larger sample size would be unlikely to affect the level of significance of the primary outcomes. A further limitation was that the bone traits in the hips and cartilage traits in the knees in relation to radiographic knee OA were not obtained from the same body part. Unfortunately, we did not have data from these bone sites due to the RCT baseline, in which the femoral neck was of interest for the purposes of screening and the main outcomes. However, this cannot be considered a critical failure, owing to the systemic disease component of both OP and OA.

In the RCT, the most pivotal study of this doctoral thesis, one limitation was that the participants were not blinded to the study groups, which is quite typical in exercise therapy studies. In addition, one the assessors (JM, author of the dissertation) was not blinded to the study. A limitation of the femoral neck bone structural measurement is that DXA-derived AHA analysis does not allow the effects of high-impact loading on redistribution of bone minerals between the trabecular component and cortical component to be distinguished, as DXA is a two-dimensional technique. While the exercise increased femoral neck bending strength but not cross-sectional area, it is plausible that training induced bone mineral redistribution from the trabecular to cortical component without any external expansion. This is supported by the finding of a cross-sectional study with female athletes representing different loading modalities that cortical bone mineral redistribution may occur from less loaded areas to more loaded areas without external expansion. Athletes representing high-impact and odd-impact types of exercise loading, such as high-jumpers and racket sport players, had clearly thicker cortices at the femoral neck than their sedentary counterparts (Nikander et al. 2009). Another limitation is that we do not know whether the positive exercise-induced changes in femoral neck bone mass and strength can be maintained in postmenopausal women after cessation of training. A previous study reported that among premenopausal women exercise-induced benefits in femoral neck strength were lost 3.5 years after the

end of the exercise intervention (Heinonen et al. 2012). A limitation related to the applied cartilage analysing technique was that occasionally thinned or deteriorated cartilage prevented reliable segmentation of the cartilage into superficial and deep layers, which might have provided more information about exercise-induced alterations in the focal cartilage. A sufficient imaging resolution would have demand a higher field strength scanner.

With regard to the daily physical activity measurements, three consecutive days of accelerometer-based recording may not be representative of habitual levels of PA. In addition, the rather crude total PA index described all the activities engaged in throughout the study, as it included the average loadings from the exercise intervention as well as daily physical activities. Furthermore, since accelerometers measure gravitational forces only, some daily physical activities may not have captured due to the meter's inability to measure static work or activities with low acceleration forces. Although these matters must not be considered of minor importance, it should be kept in mind that the accelerometer data do not provide more than a general description of daily activities and locomotion, and that the collection of the PA data was not a primary end-point but confirmed that the intensity of the intervention training was truly high.

Conversely, a definite strength of the exercise trial was that all the important quality criteria of a RCT were carefully applied. In particular, the study design was appropriately powered, which to some extent overcomes some of the research-related deficits, and the intervention was of sufficient duration. The latter is of particular importance, since one remodeling cycle takes 3 – 4 months for to complete the sequence of bone resorption, formation, and mineralization (Frost 1997). Therefore a minimum of 6 – 8 months is required to achieve a new steady-state bone mineral mass that is measurable using the current technology. Another major strength of this study was the low dropout rate. This is attributable to the fact that the training was well tolerated and a team spirit of engagement prevailed among the trainees. Furthermore, this is the first long-term trial to assess the effect of high-impact exercise directly on articular cartilage in subjects with mild knee OA by the application of quantitative MRI measures, i.e., the dGEMRIC index and T2. While standard MRI techniques have been applied for delineating cartilage morphology in few cross-sectional studies (Cicuttini et al. 2004, Brennan et al. 2011), they cannot, however, detect the initial stages of OA, including GAG loss, increased water content, and disorganization of the collagen network. Also, it was possible to quantify the impact loading of exercise with accelerometers, despite of some above-mentioned shortcomings of body movement monitoring instruments. By using the monitors we not only gained immediate feedback on the loading intensity in each training period, but would, if necessary, have been also able to adjust the loading intensity during the trial. A final strength of the study was that the statistician outside of the research group led the statistical analysis in a blinded manner.

6.5 Implications and future directions

The dGEMRIC reproducibility study showed that the accuracy of the dGEMRIC method is good, and the method is feasible for evaluating exercise-induced cartilage biochemical changes, when these changes are expected to be bigger than measurement error. The results of this study have served as indicative data for other clinical and methodological dGEMRIC experiments, and since its publication in 2009, the paper has been cited so far in over 50 articles. Currently, dGEMRIC and T2 mapping are the most established imaging tools for indirect assessments of GAG content and collagen content and orientation, and are thus important indicators for early OA (David-Vaudey et al. 2004). However, novel qMRI techniques such as T1rho mapping, sodium imaging and ultrashort echo time (UET) have emerged for cartilage imaging purposes (Matzat et al. 2013). Each technique offers its own specific information on cartilage characteristics, but looking to future research, a combination of multiple qMRI methods may provide the most comprehensive description of cartilage quality in early stage OA. The dGEMRIC field is also rapidly evolving; for instance, increasingly stronger scanner field strength (Madelin et al. 2013), automated image registration (Bron et al. 2013) and automated segmentation tools (Siversson et al. 2014) are being developed to improve imaging responsiveness and save reader time and costs. Obviously, these novel imaging and analytical tools should be applicable to other qMRI mapping methods than dGREMRIC only. In future longitudinal exercise interventions, if changes in cartilage need to be measured precisely, then it is to be hoped that new innovations in cartilage imaging technology will offer even better measurement reproducibility than today, as our training intervention, and others (Roos & Dahlberg 2005, Van Ginckel et al. 2010), have so far shown rather modest changes in cartilage quality.

In the cross-sectional association study between bones and mild knee OA, the result showed that bone mass and structural properties increased with OA severity. Theoretically, this finding suggests that mild knee OA might have a protective effect against OP. In practice, however, it is known, based on cross-sectional hip and knee studies, that as the disease progresses, the protective effect is, for some reason, lost (Soininvaara et al. 2004, Mäkinen et al. 2007, Chang et al. 2014). To elucidate the relationship between OA and OP, further prospective longitudinal follow-up investigations with subjects across the full a radiographic spectrum of OA are required. Correspondingly, with regard to bone fractures, one might expect that since knee OA is related to higher structural bone strength, this might have a protective effect against bone fractures. In part, this is true, but previous studies have shown that falling, not OP, is the strongest single risk factor for a fracture (Kannus et al. 2005, van Helden et al. 2008, Järvinen et al. 2008). Therefore, the key issue in fracture prevention is to determine which individuals are at a high risk for falls and to design preventive actions for these individuals whether they have OA or not.

Moreover, as the present study investigated bone structure with DXA at the proximal end of the femur and not in a region near the knee or at subchondral bone in the knee, future research should seek to clarify the relationship between subchondral bone and cartilage in the knee joint. The role of bone, in particular subchondral bone, in the development and progression of OA has not been fully elucidated, and there are conflicting views on whether subchondral bone alterations are the cause or a consequence of cartilage degeneration (Radin & Rose 1986, Carlson et al. 1996, Pastoureau et al. 1999, Burr & Gallant 2012). In most of those experiments bone densitometry has been performed using DXA, which renders the results somewhat dubious due to the known inaccuracies related to DXA measurements. Currently, advanced bone imaging techniques, such as CT and volumetric quantitative CT (vQCT) offer tools to assess the macrostructure of bone, whereas techniques such as high-resolution CT are applicable in vivo to assess the microstructure of trabecular bone (Genant et al. 2008). Also, T2* relaxation time of MRI has been used as a sensitive technique to assess the density of subchondral bone (Majumdar et al. 1997, Arokoski et al. 2002). To elucidate the interaction between subchondral bone and cartilage in the same joint, further investigations with advanced bone imaging techniques and subjects from all radiographic knee OA grades are needed.

On average, bone mass decreases by about 0.5% per year or more after the age of 40, regardless of sex or ethnicity (Kohrt et al. 2004). In light of this knowledge, restoring or even increasing bone mass and density in conjunction with preventive fall strategies are crucial in seeking to minimize the risk for OP in postmenopausal women. At present, pharmacological treatments are more often used than non-pharmacological treatments to increase bone mass. The non-pharmacological treatments, exercise therapy in particular, however, have advantages over pharmacological treatments by improving physical function and reducing risk for falls. In addition, after recent associations found between bisphosphonate therapy, the first-line treatment for OP, and atypical femoral fractures and osteonecrosis of the jaw (Shane et al. 2010, Borromeo et al. 2011, Borromeo et al. 2014), increasing interest has been shown by both clinicians and patients for nonpharmacological approaches to bone health. Likewise, with regard to OA, exercise is associated with relatively few side effects. Also, exercise has similar effect sizes when compared to conservative drug treatments such as nonsteroidal anti-inflammatory drugs, which may also cause serious gastrointestinal complications (Bjordal et al. 2004). In addition, recent observations about the ineffectiveness of surgical arthroscopical procedures in the treatment of OA and meniscal tears (Katz et al. 2013, Sihvonen et al. 2013) speak in favour of exercise and PA as a core treatment for knee OA. Considering the overall benefits of exercise therapy in the treatment of OP and OA, supported by the results of our high-impact exercise intervention, we suggest that bone favourable exercises can be incorporated into OA patients' exercise programs when progressively implemented. Naturally, the therapy administered to mild knee OA patients must be based on individual target

setting rather than deliberate use of high-impact loading. However, high-impact training may serve as a complementary therapy in targeting improved bone structure and physical performance without the likelihood of worsening the symptoms or posing a risk for cartilage health. We acknowledge that our results for the exercise intervention trial are based on mean values, and hence it should be borne in mind that high-impact exercises are occasionally contraindicated, although fortunately very rarely, for osteoporotic older adults at high risk for fracture. Therefore, at the outset it is important to assess the person's suitability for impact loading and also to monitor her/his progression during the rehabilitation process. Optimal exercise programs for knee OA should be supervised (Juhl et al. 2014) and group-based exercise offers the exercise instructor a practical means for monitoring exercise progression. In addition, supervised group exercises are cost-effective (Patel et al. 2014), since one exercise instructor can supervise several participants at the same time and group exercise demands on space and equipment are typically modest.

While the present study demonstrated that high-impact exercise produced benefits on bones and physical function at the 12-month endpoint of the intervention, the long-term benefits of high-impact remain uncertain, prompting the need for long post-intervention follow-ups. Also, further research is needed to determine the optimal exercise type and dose for articular cartilage. This study showed that high-impact loading is safe for articular cartilage, although it may not provide the optimal loading modality for subjects with mild knee OA. Thus, it remains to be shown whether low-impact or non-impact loading modalities, such as cycling or aquatic training have beneficial effects on articular cartilage.

7 MAIN FINDINGS AND CONCLUSION

The main findings of the study are as follows:

1. The delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) technique showed good day-to-day reproducibility in healthy subjects, with means of 5 - 8% for the different cartilage regions-of-interest. Careful training of measurement personnel and a systematic knee positioning approach are key factors affecting the precision of the results.
2. In postmenopausal women, femoral neck structure, strength and mineral mass were significantly higher, the higher the grade of radiographic knee OA, i.e., the femoral neck rigidity was associated with severity of knee OA. However, no association was observed in this population between grade of radiographic OA and estimated biochemical composition knee cartilage assessed using the quantitative MRI measures of T2 relaxation time and dGEMRIC.
3. A progressive 12-month multidirectional high-impact exercise program increased femoral neck bone mineral mass and strength, and physical performance in postmenopausal women with mild knee OA. The training had no effects on the estimated biochemical composition of knee cartilage.

In conclusion, the results of this study indicate that dGEMRIC imaging at field strength of 1.5 T can be reliably used as an instrument for the assessment of articular cartilage when the measurement personnel have been carefully trained. The results of the cross-sectional study showed an inverse relationship between OA and OP. When progressively implemented, high-impact training is a safe and feasible exercise modality in postmenopausal women with mild knee OA. High-impact training offers an effective means to decrease the risk for OP by improving femoral neck bone rigidity and by reducing physical performance-related fall-risk factors. These findings can be utilized in planning and tailoring appropriate exercise programs for the prevention of OP in postmenopausal women with mild knee OA.

YHTEENVETO (FINNISH SUMMARY)

Liikunta luustolle ja rustoille vaihdevuosi-iän ohittaneilla lievää polven nivelrikkoa sairastavilla naisilla – Vuoden kestäneen liikuntaharjoittelun vaikutukset satunnaistetussa kontrolloidussa tutkimuksessa.

Nivelrikko on maailman yleisin nivelsairaus. Erityisesti polven nivelrikko heikentää toiminta- ja liikkumiskykyä olennaisesti, koska polvinivel on painoa kantava laajat liikeradat mahdollistava nivel. Osteoporoosi eli luun haurastuminen puolestaan on salakavalasti etenevä oireeton sairaus joka pahimmillaan voi johtaa luunmurtumaan. Nivelrikon ja osteoporoosin esiintyvyys on yleisintä post-menopausaalisilla eli vaihdevuodet ohittaneilla naisilla. Tutkimustulokset ovat osin ristiriitaisia siitä, että esiintyykö molempia sairauksia yhtäaikaisesti samoilla henkilöillä, vai onko sairauksilla niin sanottu käänteinen yhteys. Tämä tarkoittaa sitä, että nivelrikkoa sairastavilla olisi keskimäärin vahvemmat luut kuin ei-nivelrikkoa sairastavilla. Väestön ikääntyessä sekä nivelrikkoa että osteoporoosia sairastavien osuus tulee lisääntymään, ja ilman nykyistä tehokkaampia hoitomenetelmiä suuret potilasmäärät tulevat kuormittamaan entistä enemmän terveydenhuoltojärjestelmäämme.

Vaikka nivelrikkoon ei ole parantavaa hoitoa, tutkimukset ovat osoittaneet että liikunnalla voidaan lievittää kipua sekä parantaa toimintakykyä ja elämänlaatua polven nivelrikkoa sairastavilla. Myös osteoporoosin hoidossa liikunta on keskeinen hoitomuoto vahvistaen sekä luiden lujuutta että vähentäen kaatumisriskiä. Jotta liikunta olisi riittävän tehokasta luun vahvistumiseksi, liikunnan tulee sisältää niveliin ja luustoon kohdistuvia korkeita kuormitushuippuja, eli iskutuksia ja nopeita suunnanmuutoksia. Tämänkaltaisen liikunnan on aiemmin arveltu olevan haitallista nivelille ja rustoille henkilöillä joilla on alkavan vaiheen nivelrikko, joskaan asiaa ei ole koskaan tieteellisesti osoitettu. Tämän väitöskirjatutkimuksen päätavoitteena oli selvittää, voidaanko iskutuksia sisältävällä hyppelyharjoittelulla vaikuttaa suotuisasti luun mineraalimassaan ja lujuuteen, sekä polviruston biokemialliseen koostumukseen vaihdevuosi-iän ohittaneille naisille, joilla on lievä polven nivelrikko. Lisäksi selvitettiin reisiluun kaulan lujuustekijöiden ja polven nivelrikon vaikeusasteen välisiä yhteyksiä vaihdevuosi-iän ohittaneilla naisilla joilla oli radiologisesti todettu polven nivelrikko sekä niillä joilla ei ollut polven nivelrikkoa. Myös polviruston kuvantamisessa käytettävän dGEMRIC magneettikuvausmenetelmän toistettavuus selvitettiin tässä väitöskirjatyössä.

Satunnaistettuun kontrolloituun liikuntatutkimukseen osallistui 80 lievää polven nivelrikkoa sairastavaa 50 - 65 -vuotiasta naista, joista puolet arvottiin harjoitusryhmään (n = 40) ja puolet ei-harjoittelevaan kontrolliryhmään (n = 40). Liikunnan vaikutuksia luustoon mitattiin kaksienergisella röntgenabsorptiometrilla (DXA) ja polvinivelen (reisiluu-sääriluuliitos) rustoihin kvantitatiivisen magneettikuvantamisen dGEMRIC ja T2 relaksaatioaikamenetelmillä. Lisäksi selvitettiin liikunnan vaikutuksia lihasvoimaan, dynaamiseen tasapainoon ja kestävyyskuntoon, sekä kliinisesti merkittäviin

oireisiin WOMAC -kyselylomakkeen avulla. Vuoden kestänyt liikunta-interventio ja suurin osa mittauksista toteutettiin Jyväskylän yliopistossa terveystieteiden laitoksella. Osa mittauksista ja tulosanalyyseistä tapahtui Keski-Suomen keskussairaalassa, Oulun yliopistollisen sairaalan radiologian klinikalla sekä Oulun yliopiston lääketieteen tekniikan laitoksella, jotka toimivat hankeen yhteistyökumppaneina.

Reisiluun kaulan lujuustekijöiden ja polven nivelrikon vaikeusasteen välisiä yhteyksiä tarkastelevaan poikkileikkaustutkimukseen osallistui 12 vaihdevuosi-iän ohittanutta tervepolvista naista. Yhdistämällä tervepolvisten ja liikuntatutkimukseen osallistuneiden lievää polven nivelrikkoa sairastaneiden naisten alkutilanteen tiedot, selvitettiin onko nivelrikkoa sairastavien naisten luut vahvempia kuin tervepolvisten naisten luut. Polviruston kuvantamisessa käytettävän dGEMRIC -kuvausmenetelmän toistettavuus selvitettiin ennen liikuntatutkimusta kolmen, keskimäärin viiden päivän välein tehdyn mittauksen avulla yhteensä kymmenelle oireettomalle nuorelle naiselle ja miehelle.

dGEMRIC menetelmätyö osoitti että eri testauskertojen välistä toistettavuutta kuvaava variaatiokerroin oli keskimäärin 5 - 8 % tarkasteltavasta rustoalueesta riippuen. Käytännössä tämä tarkoittaa sitä, että dGEMRIC kuvausmenetelmän toistettavuus on hyvä, ja että menetelmä soveltuu tutkimuskäyttöön silloin kun mittaajien koulutukseen ja polven huolelliseen asetteluun on kiinnitetty erityistä huomiota. Luuston lujuuden ja nivelrikon radiologisen vaikeusasteen välisiä yhteyksiä tarkasteltaessa havaittiin että reisiluun kaulan poikkipinta-ala, taivutuslujuus sekä mineraalimassa olivat sitä suurempia, mitä pidemmälle radiologinen polven nivelrikko oli edennyt vaihdevuosi-iän ohittaneilla naisilla. Löydös viittaa nivelrikon ja osteoporoosin väliseen käänteiseen yhteyteen, joskaan tuloksemme ei pysty tätä täysin vahvistamaan, koska liikuntatutkimuksen tiukkojen sisäänottokriteerien takia tutkimusjoukosta puuttuivat sekä osteoporoosia että vaikeaa polven nivelrikkoa sairastavat henkilöt.

Liikuntatutkimuksen tulokset osoittivat että vuoden kestänyt säännöllinen hyppelyharjoittelu lisäsi harjoitusryhmällä reisiluun kaulan mineraalimassaa ja lujuutta, kun ne puolestaan alenivat tavanomaista liikuntakäyttäytymistä jatkaneella kontrolliryhmällä. Lisäksi tasapaino, lihasvoima ja kestävyyskunto, jotka kaikki ovat keskeisiä tekijöitä kaatumistapaturmien ehkäisemisessä, paranivat merkitsevästi enemmän harjoitus- kuin kontrolliryhmällä. Sen sijaan polvirustossa tai kliinisesti merkittävissä oireissa ei tapahtunut ryhmien välisiä muutoksia. Harjoittelu oli kaiken kaikkiaan hyvin siedettyä ja tutkimuksesta poispudonneiden määrä oli alhainen (4 henkilöä, 5 %). Näiden tulosten perusteella progressiivisesti toteutettava iskutuksia sisältävä hyppelyharjoittelu näyttäisi soveltuvan henkilöille joilla on lievä polven nivelrikko sekä alentunut luuntiheys tai epäilys siitä. Koska intensiivinen hyppelyharjoittelu ei aiheuttanut muutosta polviruston biokemiallisessa koostumuksessa suuntaan tai toiseen, kyseinen harjoitusmuoto ei välttämättä ole kuitenkaan optimaalisin harjoitusmuoto lievässä polven nivelrikossa. Tämän takia tarvitaankin jatkotutkimuksia selvittämään miten rustoa vähemmän kuormittavat lajit, kuten

uinti tai pyöräily vaikuttaa polviruston biokemialliseen koostumukseen lievää polven nivelrikkoa sairastavilla henkilöillä.

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ORIGINAL PAPERS

I

REPRODUCIBILITY OF IMAGING HUMAN KNEE CARTILAGE BY DELAYED GADOLINIUM-ENHANCED MRI OF CARTILAGE (dGEMRIC) AT 1.5 TESLA

by

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Reproducibility of imaging human knee cartilage by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5 Tesla

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Summary

Objective: The purpose of this study was to investigate the day-to-day reproducibility of the delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) measurement at different knee joint surfaces in healthy subjects at 1.5 Tesla (T).

Methods: The dGEMRIC experiment was repeated for 10 asymptomatic volunteers three times with an average interval of 5 days between scans. The measurement was performed from a single sagittal slice through the center of the lateral femoral condyle and from the center of the patella in the axial plane. Cartilage was manually segmented into superficial, deep and full-thickness regions of interests (ROIs) at different topographical locations of the femur, tibia and patella. The reproducibility was evaluated separately for each ROI as well as for the entire bulk cartilage in the slice of each joint surface.

Results: The reproducibility at various ROIs expressed by root-mean-square average coefficient of variation (CV_{RMS}) ranged between 4.7–12.9%. Thirty out of thirty-three ROIs showed a CV_{RMS} less than 10%. Intraclass correlation coefficient (ICC) ranged between 0.45 and 0.98. The CV_{RMS} and ICC for bulk dGEMRIC were 4.2% and 0.95 for femur, 5.5% and 0.87 for tibia, and 4.8% and 0.97 for patella.

Conclusions: The dGEMRIC technique showed good day-to-day reproducibility, on the average 8% for small deep or superficial segments, 7% for full-thickness ROIs and 5% for bulk ROIs covering all visible cartilage in a single joint surface. We conclude that dGEMRIC imaging at field strength 1.5 T can be used as a reliable instrument for the assessment of articular cartilage when staff has been carefully trained.

Key words: dGEMRIC, Reproducibility, Cartilage, Proteoglycan, Knee joint.

Introduction

Osteoarthritis (OA) is a multifactorial age-dependent musculoskeletal disease that has been estimated to affect 1 in 10 at age 50 and >1 in 2 at age 75[1]. Knee OA is commonly associated with severe disability because the knee joint is a weight-bearing joint with a large range of motion. The assessment of the articular cartilage, the key factor of the early pathological changes of OA, is of great importance for diagnosing and monitoring the joint status.

Although plain radiographs are a cost-effective means to evaluate the joint status, it does not offer direct information about the articular cartilage[2]. Magnetic resonance imaging (MRI) is applicable for achieving morphological data i.e., volume, thickness and curvature of the cartilage. In practise, it provides information about the current status of cartilage or acute variations in relation to interventions or diseases. However, early histological and biochemical changes cannot be detected using standard MR techniques.

The early phase of degenerative process in cartilage is expressed by the loss of glycosaminoglycan (GAG) macromolecules from the matrix[3–5] with an associated deterioration in the mechanical properties of cartilage[6]. The delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) technique can be used to indirectly assess the distribution of GAGs in cartilage[7]. dGEMRIC utilizes an anionic contrast agent chelate Gd-$DTPA^{2-}$ that opposes the negative charge of GAGs. Thus, after intravenous administration of Gd-$DTPA^{2-}$ the contrast agent is distributed into cartilage in inverse relation to GAGs. Due to the ability of Gd-$DTPA^{2-}$ to shorten the T1 relaxation time in proportion to its concentration, T1 relaxation time measurements provide a means to indirectly assess the GAG content of cartilage. The technique has been histologically validated *in vitro*[8,9] and it has been applied in several *in vivo* studies and orthopaedic patient populations[10–19]. The technique is promising in evaluating the biochemical progression of disease and effects of therapeutic interventions especially in the early phase of OA when focal defects are not yet visible by any other means[20,21].

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While the dGEMRIC technique has been applied in various *in vivo* human studies, the knowledge of its reproducibility has been very limited. To our knowledge, only a single study addresses dGEMRIC reproducibility, where a measurement reproducibility of 10–15% is reported[11]. Only five knees from three subjects were measured using either double or single dose contrast agent injection twice at the interval from 2 weeks to 2 months.

Due to the apparent lack of systematically designed dGEMRIC reproducibility studies, the aim of the present study was to evaluate the day-to-day reproducibility of the dGEMRIC measurements in human knee cartilage of asymptomatic volunteers.

Methods

PARTICIPANTS

Ten asymptomatic volunteers (five females and five males) were recruited from the University of Jyväskylä in Finland. Their mean age was 31.7 (standard deviation (SD) 6.4; range 25–47) years, mean height 174.4 (9.3; 161–187) cm, mean weight 77.4 (16.4; 58–113) kg and mean body mass index (BMI) 25.3 (3.5; 22–34) kg/m^2.

The inclusion criteria were: willingness to participate, healthy, age of 18 years or more, no history of knee injury or surgery and no knee-related symptoms. A participant was excluded if she or he had electronically, magnetically and mechanically activated implants; hemostatic clips; wires; ocular foreign bodies; tattoos; congestive heart failure; claustrophobia, any known allergies to contrast agents or she was pregnant or breastfeeding. In addition, the participants' eligibility was confirmed by MRI routine diagnostic series to exclude structural changes in the knee.

All participants were physically active, their physical activity level varied from one to seven times per week training sessions lasting from 1 to 10 h per week. The most common exercises were walking, running, swimming, floor-ball, and strength training. Written informed consent was obtained from all participants and the study was approved by the Ethics Committee of the Central Finland Health Care District.

PROTOCOL

The day-to-day reproducibility measurements of the knee cartilage were performed three times by four technicians within an average 5.3 (SD 3.0) days between imaging sessions. In the first imaging session, the MRI scans included both standard MRI series and dGEMRIC mapping. The second and third session only consisted of the dGEMRIC experiment. For all three measurements, participants were measured at the same time of the day within the limits of 2 h to minimize the effect of diurnal variation. dGEMRIC was performed 90 min after intravenous injection of contrast agent. The participants were asked to avoid any strenuous physical activity before or on the day of the imagining. The subjects were weighed before every MRI measurement to assure a correct injection dose of contrast agent. The body weight did not vary between the three imaging sessions.

The right patellar, femoral and tibial cartilages were scanned with a General Electric Signa CV/i 1.5 T MR imaging system (GE Medical Systems, Waukesha, Wisconsin) with an 8-channel HD transmit/receive knee array coil (*In vivo* corporation, Gainesville, FL, USA) with application of a standard shim procedure. The participants were imaged in supine positioning. The knee was positioned into the coil by adjusting inferior margin of patella according to centre line of the coil. The flexion angle and rotation of the knee was controlled by stabilizing the ankle to a fixed position with the medial side of the ankle vertically with the use of a leg holder and a custom-made inflatable cushion to fix the joint within the knee coil. The cushion was set over the knee with the patella positioned into the circular hole of the cushion. The pressure in the cushion was adjusted individually to stabilize the knee inside the coil firmly but comfortably.

MRI

On the first session the following clinical MRI series were imaged: a sagittal proton density-weighted fast spin echo sequence (repetition time (TR) 4000 ms; echo time (TE) 13 ms; echo train length (ETL) 8; field of view (FOV) 160 mm; acquisition matrix 384 × 256; 3 mm slice thickness), a sagittal T2-weighted fast spin echo sequence (TR/TE 4200/89 ms; ETL 15; FOV 160 mm; 384 × 224 matrix; 4 mm slice thickness), a coronal T2-weighted fast spin echo sequence with fat suppression (TR/TE 3400/67 ms; ETL 8; FOV 160 mm; 384 × 256 matrix; 4 mm slice thickness), an axial proton density-weighted sequence with fat suppression (TR/TE 4000/14 ms; ETL 8; FOV 160 mm; 384 × 256 matrix; 4 mm slice thickness) and a coronal T1-weighted spin echo sequence (TR/TE 540/10 ms; FOV 160 mm; 384 × 224 matrix; 4 mm slice thickness).

For the dGEMRIC experiment, a double dose i.e., 0.2 mM/kg (0.4 ml/kg) injection of Gd-DTPA^{2-} (Magnevist, Schering Ag, Berlin, Germany) was administered through the veins of the antebrachium or hand. Thereafter, the subject performed active flexion-extension exercises of the knee for 5 min while sitting on the edge of a table and 5 min walking to increase the delivery of contrast agent into the cartilage[22,23]. T1-mapping was performed using a single-slice inversion recovery fast spin echo sequence (TR/TE 1800 ms; TE 13 ms; TI = 1600, 800, 400, 200, 100 and 50 ms; ETL 5; 3 mm slice thickness; 384 × 288 matrix; FOV 140 × 105 mm, 0.36 × 0.36 mm in-plane resolution, 41.67 kHz receiver band-width) with approximately 10.5 min imaging time per series.

The procedure for single dGEMRIC slice positioning was as follows. The three-plane scout view included nine slices in each direction. The sagittal dGEMRIC slice was positioned perpendicular to a line tangential to posterior femoral condyles in the axial scout view. To obtain this orientation, a multislice sequence was localized first, and the number of the slices in the correct orientation was reduced to one. The remaining slice was then positioned at the center of the lateral condyle as viewed on the axial scout image. In the axial plane, the procedure was similar i.e., multiple slices were positioned parallel to a line tangential to posterior femoral condyles in the axial scout view and the remaining single slice was positioned at the center of the patella in the sagittal scout view.

dGEMRIC ANALYSIS

The presence of intact cartilage surfaces was verified by a musculoskeletal radiologist (R.O.) from the clinical MR images of the first imaging session. This was followed by dGEMRIC analysis using a mono-exponential fitting routine in Matlab (version 7.2, Mathworks, Natick, MA, USA). Femoral, tibial and patellar cartilage surfaces were divided for regions of interest (ROI) analyses according to a scheme modified from Eckstein *et al.* (2006)[24] (Fig. 1). In the sagittal plane, the central lateral femoral condyle was divided into six segments and lateral tibial condyle was divided into three segments. In the axial plane, the central patellar cartilage was divided into two segments from the apex. Each segment was further divided into separate ROIs for the superficial and deep halves of cartilage thickness. Full-thickness dGEMRIC values were also determined for each segment. Finally, bulk values for the entire cartilage at each joint surface were computed.

STATISTICAL ANALYSIS

As the measure of dGEMRIC reproducibility for the different segments (superficial and deep 50% of tissue, full-thickness and bulk) the coefficient of variation (CV), representing the percentual magnitude of day-to-day variability, was determined for each ROI of each volunteer. To depict the reproducibility for the population root-mean-square average coefficient of variation (CV_{RMS}) was calculated for each ROI according the formula: $CV_{RMS} = \sqrt{\sum (CV)^2/n}$, where n = number of subjects. CV_{RMS} values less than 10% were interpreted as good, and values below 5% were considered very good[25]. In addition, the day-to-day reproducibility was determined using intraclass correlation coefficient (ICC), representing the error-free proportion of the inter-subject score variation with 95% confidence interval (CI). ICC values above 0.75 were interpreted as good, whereas values between 0.74 and 0.40 indicated moderate and values below 0.40 indicated poor reliability[26]. The statistical analyses were performed by using SPSS software (version 14, SPSS Inc, Chicago, IL, USA). The average T1 value at each cartilage segment was determined as the average of the mean T1 value of three measurements.

Results

All 10 subjects took part in all three consecutive measurements. Eight ROI segments from the first measurement session could not be analyzed due to aliasing artefact in medial patellar superficial and deep segments of two participants, and anterior and posterior aspect of the trochlea from superficial and deep segments of one participant.

In clinical MRI series the participants had two medial and two lateral facet thinning cases in the patella, three superficial fissure cases in the apex of the patella, one superficial fissure in the medial condyle, one confirmed and one suspected chondromalasia of the patella, one patella alta, one mild hydrops and Baker's cyst, one degeneration of the posterior horn of the medial meniscus and one laterally tilted patella. No one had cartilage changes in the lateral

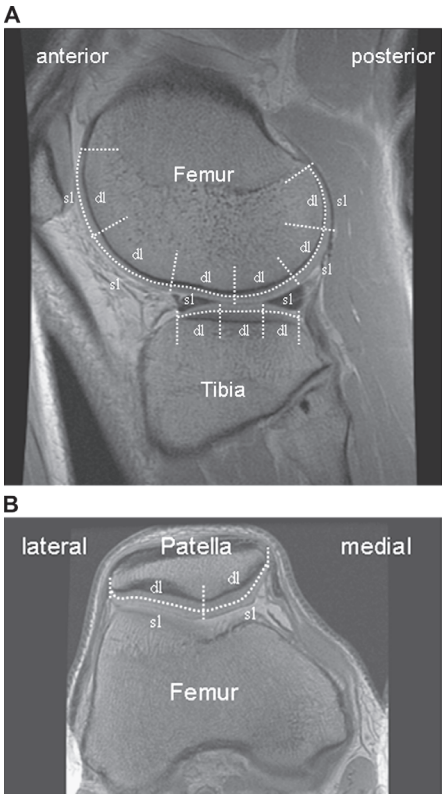

Fig. 1. Segmental division of femoral, tibial and patellar cartilages into ROIs. There is a visible aliasing artefact in both images; in sagittal imaging plane (A) anteriorly and in the axial imaging plane (B) on down on the lateral and medial sides. These artefacts had no influence on data analyzing because they did not overlap with the ROIs. Superficial and deep layers are indicated with ''sl'' and ''dl'', respectively.

femoral condyle, where the dGEMRIC data was collected. One participant had mild thomboflebitis at the site of the injection. The irritation of the vein faded by the second measurement session, and did not appear afterwards.

SEGMENTAL REPRODUCIBILITY

The mean T1 relaxation time and reproducibility results (CV_{RMS} and ICC values) for all analyzed cartilage segments are presented in Table I. The precision error (CV_{RMS}) ranged from 4.7% to 12.9% for superficial and deep ROI segments and from 4.8% to 11.6% for full-thickness ROIs. The precision was good in terms of CV_{RMS} (less than 10%) at patellar and tibial segments and from good to fair at femoral segments. For superficial and deep ROIs, and for full-thickness dGEMRIC values the precision error was generally the lowest at central segments in femoral and tibial cartilage, except for the anterior aspect of trochlea. In patella, the precision error was the lowest in the lateral segment of cartilage. Furthermore, the precision errors were somewhat lower at the superficial half than at deeper half of cartilage in femur and patella.

The ICC of dGEMRIC values in the femoral, tibial and patellar cartilage segments ranged widely from 0.45 to 0.98 (Table I). The best ICCs were among patellar ROIs (range 0.94–0.98). The ICC was good at all other segments but deep anterior and posterior central segments of the femur, superficial and deep posterior segments of the posterior

Table I
Mean T1 relaxation time (SD), CV_{RMS} and ICC for superficial, deep and full-thickness cartilage segments in the femur, tibia and patella

Cartilage segment	*n*	T1 (ms)	CV_{RMS} (%)	ICC (95% CI)
Lateral femoral condyle				
Anterior aspect of trochlea				
Superficial layer	9	420.5 (5.3)	6.1	0.92 (0.74–0.98)
Deep layer		479.2 (21.4)	9.2	0.89 (0.65–0.97)
Full-thickness		447.8 (12.7)	6.9	0.91 (0.73–0.98)
Posterior aspect of trochlea				
Superficial layer	9	384.7 (4.1)	7.1	0.93 (0.77–0.98)
Deep layer		447.5 (14.3)	9.9	0.91 (0.72–0.98)
Full-thickness		412.9 (7.9)	7.8	0.92 (0.77–0.98)
Anterior central part				
Superficial layer	10	448.2 (8.9)	7.0	0.86 (0.60–0.96)
Deep layer		456.4 (4.1)	9.1	0.68 (0.01–0.92)
Full-thickness		452.0 (4.0)	7.1	0.80 (0.41–0.95)
Posterior central part				
Superficial layer	10	525.6 (13.7)	5.2	0.84 (0.55–0.96)
Deep layer		558.7 (4.5)	7.2	0.45 (−0.77–0.86)
Full-thickness		540.9 (6.7)	4.8	0.81 (0.46–0.95)
Anterior posterior part				
Superficial layer	10	443.5 (12.5)	8.7	0.77 (0.35–0.94)
Deep layer		530.3 (18.7)	6.8	0.90 (0.70–0.97)
Full-thickness		481.2 (11.0)	6.8	0.88 (0.66–0.97)
Posterior posterior part				
Superficial layer	10	359.0 (8.2)	11.9	0.51 (−0.51–0.87)
Deep layer		405.4 (19.9)	12.9	0.67 (0.09–0.91)
Full-thickness		379.0 (12.5)	11.6	0.62 (−0.08–0.90)
Lateral tibial condyle				
Anterior part				
Superficial layer	10	420.0 (1.0)	9.3	0.88 (0.65–0.97)
Deep layer		460.9 (10.0)	8.3	0.76 (0.32–0.94)
Full-thickness		436.9 (3.3)	6.9	0.89 (0.68–0.97)
Central part				
Superficial layer	10	443.4 (7.0)	7.5	0.90 (0.72–0.97)
Deep layer		523.5 (2.8)	5.8	0.75 (0.24–0.93)
Full-thickness		477.8 (5.5)	6.0	0.88 (0.64–0.97)
Posterior part				
Superficial layer	10	416.6 (5.6)	6.2	0.91 (0.74–0.98)
Deep layer		510.6 (7.7)	7.4	0.45 (−0.70–0.85)
Full-thickness		454.5 (6.6)	5.8	0.83 (0.51–0.95)
Patella				
Medial aspect				
Superficial layer	8	409.8 (10.9)	7.6	0.95 (0.83–0.99)
Deep layer		498.9 (17.3)	8.3	0.94 (0.80–0.99)
Full-thickness		449.2 (14.3)	6.1	0.96 (0.85–0.99)
Lateral aspect				
Superficial layer	10	437.8 (2.4)	4.7	0.98 (0.94–0.99)
Deep layer		535.3 (7.5)	7.0	0.97 (0.92–0.99)
Full-thickness		482.3 (3.5)	5.0	0.98 (0.94–0.99)

femur and deep posterior segment of the tibia. The ICC values were higher in superficial half as compared to deep half of the tissue except for the posterior part of the femur.

BULK REPRODUCIBILITY

The reproducibility of the bulk dGEMRIC value was good to excellent for different joint surfaces. The precision errors (CV_{RMS}) for femoral, tibial and patellar cartilage were 4.2% ($n = 9$), 5.5% ($n = 10$) and 4.8% ($n = 8$), respectively. The corresponding ICC values for the femur, tibia and patella were 0.95 (95% CI 0.85−0.99), 0.87 (0.61−0.96) and 0.97 (0.90−0.99), respectively.

Discussion

To our knowledge this was the first study investigating systematically and exclusively the reproducibility of knee cartilage dGEMRIC measurements. In general, the precision of dGEMRIC at 1.5 T turned out to be good. When the mean T1 relaxation time of the whole joint surface in the imaging slice was assessed (i.e., bulk analysis), two out of three joint surfaces had CV_{RMS} values less than 5%, which is considered to be very good. Also, in the segmental analysis, ROIs had a CV_{RMS} mostly less than 10%. This represents substantially higher measurement accuracy as compared to that presented by Burstein *et al.*[11]. They reported that T1 relaxation times had reproducibility within 10−15% calculated as the ratio between the second and first dGEMRIC scan with a limited number of subjects with up to 2 months interval[11]. The lower measurement accuracy of Burstein *et al.* compared to our results may be explained by the low sample size and the imaging performed several weeks apart. It has been suggested that CV_{RMS} values lower or equal to 10% signifies good measurement reliability[27]. CV values approximately 5% are considered an excellent reliability in conventional radiology in repeated analysis of knee joint space narrowing[28]. For comparison, earlier MR imaging studies of cartilage have shown that *in vivo* reproducibility is in the range 1−5% for cartilage volume[29−32] and 3−6% for mean thickness[31−33]. The dual energy absorbtiometry (DXA) technique has a reproducibility of 1−3% in determining bone mineral density (BMD) at various skeletal sites[34−37], while peripheral quantitative computed tomography (pQCT) is in range 1−8% for the density and area of long bones[38]. T2 relaxation time measurements of articular cartilage in the patella show a CV of 3−7% for global and 6−29% for regional ROIs at 1.5 T[39], while the ankle joint show a reproducibility of 3−5%[40].

In addition to the CV, the ICC generally showed good reliability in the segmental analysis. Twenty-seven out of 33 segments had ICC value considered as good reproducibility. However, among six segments the ICC values were rather low with wide CIs. The ICC analysis suggests that the precision error of the measurement is related with the testers or the method. In the dGEMRIC method, this may be at least partly explained by thin cartilage and small segment area that have fewer pixels and also the possibility of partial volume effect. This is supported with our finding that in the bulk value analysis the average ICC exceeded the value 0.9, which is considered as high measurement reliability[25]. Thicker patellar cartilage showed also better measurement accuracy than thinner cartilage in femur and tibia. That is, patella has larger ROIs and bulk areas with more pixels as compared to smaller areas and fewer pixels in femoral and tibial cartilages.

Positioning of the knee is a definite source of error in quantitative MR imaging of cartilage. In the present axial images, we observed some inter-individual variability in leg rotation despite careful positioning of the knee into the coil and use of adjustable cushions. Positioning error of the knee due to rotation probably causes less positioning error in patellar ROIs in the axial plane than in the scans of femur and tibia. This may be another reason for good accuracy in the dGEMRIC measurement of the patella. Based on our experience, careful technician training is of great importance. Reference to the images of the prior imaging session plays also an important role in slice positioning.

When comparing the reproducibility of superficial and deep ROIs, the measurement of superficial ROIs predominantly showed to be somewhat better than deeper ROIs with the exception of tibial cartilage. This is attributable to the reason, that the boundary between cartilage's surface and synovial cavity in superficial ROIs can be differentiated more accurately due to greater contrast than the boundary between subchondral plate and calcified cartilage in deep ROIs which is not very distinct on proton density or T1-weighted images. For deep ROIs in tibial cartilage, segmentation of the cartilage−bone interface and deep cartilage signal can be affected by chemical shift that results in misregistration of fat signal by two pixels on the water signal from cartilage.

The delineation of the cartilage surface and cartilage−bone interface may also affect the division of cartilage into superficial and deep halves, since the division was performed manually. This can possibly affect the mean T1 values for both superficial and deep ROIs since the dGEMRIC index is known to vary with cartilage depth as a reflection to the depth-wise gradient in proteoglycan content[9]. Interestingly, Glaser *et al.* reported worse reproducibility of T2 quantitation for superficial cartilage and attributed this to the differences between T2 of cartilage and joint fluid[39]. For dGEMRIC, synovial fluid has a T1 relaxation time closer to that of cartilage and thus is not likely to contribute to reproducibility in such as extent. The bulk dGEMRIC measurements are not affected by inaccuracies in segmental division and thus accuracy is improved. The result of large ROIs having good measurement accuracy is supported by the study of Tiderius *et al.*[41], in which large lateral and medial cartilage ROIs in the load-bearing cartilage had segmentation reproducibility as good as 2.6% and 1.5%, respectively. Nevertheless, it is important to be able to analyze cartilage in small segments accurately, since patients with OA do not loose cartilage uniformly, but primarily at certain locations[42]. The delineation of ROIs for dGEMRIC or other quantitative relaxation time maps could be further improved by using segmentation from higher cartilage contrast sequences as a mask.

Previously, division of the cartilage surface into three zones with cartilage depth has been proposed for MRI studies[24,39]. For cartilage surfaces with thick tissue and sufficient imaging resolution, such as the patella, this may be feasible, however, in the light of the present results the effect of division into three zones is likely to further decrease the accuracy of relaxation time quantitation. Thus, the reproducibility should be determined separately for each approach. For thinnest cartilage surfaces division into more than two zones is clearly not feasible if reasonable precision error is desired.

There are some limitations in this study. The sample size was relatively small, however, we performed three measurement sessions for each subjects in separate days. Also, manual segmentation may have limited the reproducibility, since semi-automated segmentation of cartilage

volume has been shown to reach a higher accuracy in cartilage plate analysis as compared to manual segmentation[43]. Another limitation may have been the field strength used. Recently, higher reproducibility of cartilage volume and thickness was reported for 3.0 T field strength as opposed to 1.5 T[44]. Higher signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) at 3.0 T may further improve the cartilage segmentation precision in the dGEMRIC experiment. Further, only asymptomatic volunteers were assessed. It is unclear whether results of asymptomatic participants would also apply to OA patients. The delineation of the cartilages may be more difficult due to fibrillation of the articular surface and deconstruct of cartilage among patients with OA. This assumption is supported by the previous work of Glaser *et al.* (2003), in which they observed a better reproducibility of femoral cartilage volume measurements from coronal MR images of healthy volunteers compared to patients with severe OA[45]. While some of the participants in our study had several minor cartilage and joint alterations, the ROIs could be defined rather promptly, also the clinical findings can be assumed to have little effect into measurement precision error. The reproducibility in more progressed joint and cartilage degeneration remains to be shown. For strongly obese patients the standard knee coil or bore may not always be feasible because of large knee or body diameter.

The clinical significance of this work is that, in terms of reproducibility, dGEMRIC can be used as a reliable instrument for the assessment of articular cartilage. In clinical practice and interventions the effects to the cartilage are expected to be small, however, dGEMRIC appears to be sensitive enough to detect such changes[46]. The results of the present study can be utilized as a piece of indicative data for future reproducibility dGEMRIC trials in different groups to be studied. Based on our clinical experience, careful staff training and a systematic positioning approach are essential for the measurement precision. Further studies are required to demonstrate the reproducibility of the dGEMRIC method with patients having severe structural alterations in their cartilages, for different three-dimensional sequences that have recently become available[18,47,48] and for higher field strengths.

In summary, the dGEMRIC technique showed good day-to-day reproducibility, on the average 8% for small deep or superficial segments, 7% for full-thickness ROIs and 5% for bulk ROIs covering all visible cartilage in a single joint surface. Reproducibility is affected by both joint-related factors, such as positioning of joint and timing of contrast agent injection, and imaging-related factors, such as slice positioning, accuracy of segmentation and partial volume effect. We conclude that dGEMRIC imaging at field strength of 1.5 T can be used as a reliable instrument for the assessment of articular cartilage when staff has been carefully trained.

Conflict of interest

There is no conflict of interest between the authors and financial or personal relationship with other people or organizations according to this study.

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II

BONE AND CARTILAGE CHARACTERISTICS IN POSTMENOPAUSAL WOMEN WITH MILD KNEE RADIOGRAPHIC OSTEOARTHRITIS AND THOSE WITHOUT RADIOGRAPHIC OSTEOARTHRITIS

by

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Original Article

Hylonome

Bone and cartilage characteristics in postmenopausal women with mild knee radiographic osteoarthritis and those without radiographic osteoarthritis

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Abstract

Objectives: To evaluate the association between radiographically-assessed knee osteoarthritis and femoral neck bone characteristics in women with mild knee radiographic osteoarthritis and those without radiographic osteoarthritis. **Methods:** Ninety postmenopausal women (mean age [SD], 58 [4] years; height, 163 [6] cm; weight, 71 [11] kg) participated in this cross-sectional study. The severity of radiographic knee osteoarthritis was defined using Kellgren-Lawrence grades 0=normal (n=12), 1=doubtful (n=25) or 2=minimal (n=53). Femoral neck bone mineral content (BMC), section modulus (Z), and cross-sectional area (CSA) were measured with DXA. The biochemical composition of ipsilateral knee cartilage was estimated using quantitative MRI measures, T2 mapping and dGEMRIC. The associations between radiographic knee osteoarthritis grades and bone and cartilage characteristics were analyzed using generalized linear models. **Results:** Age-, height-, and weight-adjusted femoral neck BMC (p for linearity=0.019), Z (p for linearity=0.033), and CSA (p for linearity=0.019) increased significantly with higher knee osteoarthritis grades. There was no linear relationship between osteoarthritis grades and knee cartilage indices. **Conclusions:** Increased DXA assessed hip bone strength is related to knee osteoarthritis severity. These results are hypothesis driven that there is an inverse relationship between osteoarthritis and osteoporosis. However, MRI assessed measures of cartilage do not discriminate mild radiographic osteoarthritis severity.

Keywords: Osteoarthritis, Bone Strength, Kellgren and Lawrence Grade, Quantitative MRI, Postmenopausal Women

Introduction

Osteoarthritis (OA) and osteoporosis (OP) may cause serious morbidity and impose a substantial burden on the health care system, especially among elderly women. Although OA affects all of tissues within a joint, a characteristic aspect of an osteoarthritic joint is a progressive degeneration of articular cartilage. In OP, the related bone loss leads to an increased risk of fracture. The relationship between these two diseases is not well understood and is a topic of controversy[1].

Even though clinical experience and some studies indicate that OA and OP are not mutually exclusive[2], previous reports, including large epidemiological studies and subsequent cross-sectional studies, suggested that OA is associated with higher bone mineral mass or density[3-6]. Moreover, subjects with OA seem to not only have higher bone mineral mass, but also bigger bone size compared with healthy controls[7]. Also, women with OA are observed to have larger muscle mass and force compared with age- and body size-matched osteoporotic women[8]. From the perspective of bone and cartilage interac-

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tion, there is some evidence showing that bone mineral mass is associated with knee cartilage volume in healthy adults[9,10]. In a longitudinal analysis, bone loss was associated with loss of cartilage volume in subjects with knee OA[11].

In addition to cartilage volumetric assessment, recent advances in quantitative magnetic resonance imaging (qMRI) techniques have enabled the use of biomarkers for structure and biochemical composition of cartilage. T2 relaxation time mapping is a qMRI technique sensitive to the integrity of the collagen network, collagen orientation, and hydration[12], whereas the delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) is sensitive to cartilage glycosaminoglycan (GAG) content[13-15]. Analogously, in order to be able to analyze bone structure and strength, software for dual energy x-ray absorption meter (DXA) and advanced hip structure analysis (AHA) were developed to derive hip geometry from bone mineral data for an estimate of hip strength[16]. Thus, concurrent use of qMRI and AHA provides potential tools for determining the biochemical composition of cartilage, and assessing bone structure and strength prior to gross morphologic changes of cartilage or bone fracture have occurred. However, to our knowledge there are no studies in subjects with mild OA and who may be at risk of OP focused on bone mass and strength and cartilage biochemical composition. Therefore, the aim of the present study was to investigate the association between radiographic knee OA with femoral neck bone characteristics using AHA in a sample of postmenopausal women with mild knee radiographic OA and those without radiographic OA.

Materials and methods

Study participants

Baseline data from the previously reported randomized controlled trial (RCT)[17] with two trial arms: 1) a high-impact exercise and 2) a nonintervention were used in the current cross-sectional study. Seventy-eight postmenopausal women with mild knee OA were recruited via newspaper advertisement from the Central-Finland area. During the screening process of study participants, knee OA was radiographically confirmed at the symptomatic or most symptomatic knee. Subjects with Kellgren-Lawrence (K/L) grade 1 or 2 radiographic OA changes[18] in the tibiofemoral joint were included, while subjects with moderate or severe knee OA (K/L grades 3 or 4) were excluded after screening process. In addition of having knee K/L grade 1 or 2, other eligibility criteria for the RCT and the current cross-sectional study were postmenopausal status, age 50-65 years, knee pain on most days within the preceding year, no more than twice weekly regular intensive exercise, and no illness that contraindicated or limited participation in the exercise intervention. A subject was excluded if her T-score for femoral neck bone mineral density (BMD, g/cm^2) was lower than -2.5; body mass index (BMI, kg/m^2) was higher than 35 kg/m^2; and if she had any previous knee instability or severe trauma, inflammatory joint disease, or knee intra-articular steroid injections in the preceding 12 months. Moreover, a subject was excluded if she had any known contraindications to MRI, any known allergies to contrast agents, or renal insufficiency. Additionally, an age-, weight-, and height-matched sample of 12 women with no considerable knee symptoms were recruited to the study as a reference group from the same source population as those who were recruited into the parent RCT. The inclusion and exclusion criteria were same as for the women with mild knee OA, except that the women without clinically significant symptoms should not have had any frequent pain, aching or stiffness in or around the knee joint in either knee in the preceding year. The suitability of the women without significant symptoms was confirmed by the radiographs, and only subjects who had no radiographic OA changes (i.e., K/L grade 0) in both tibiofemoral joints were entered into the study. The exercise study protocol with the amendment of the study protocol of women without significant symptoms and radiographic OA (hereafter called K/L 0 group) were in agreement with Helsinki declaration with the approval of the Ethics Committee of the Central Finland Health Care District. Written informed consent was obtained from all participants prior to enrollment.

Knee radiography

The radiographs were acquired during screening examinations from both knees with a postero-anterior view of the tibiofemoral joint in a semi-flexed weight-bearing position. An experienced musculoskeletal radiologist blinded to subjects graded the X-rays according the radiological grading scale of Kellgren and Lawrence (K/L). This system uses the following global grades (for tibiofemoral OA): 0 = normal, 1=doubtful (possible osteophytes), or 2=minimal (definite osteophytes, possible joint space narrowing)[18]. In subjects with OA, the final grade was the highest one for the most severely-affected knee.

Bone assessment

Proximal femurs were scanned with dual-energy X-ray absorptiometry (DXA, GE Medical System, Lunar Prodigy, Madison WI, USA) at the narrowest femoral neck section from the side of the higher K/L grade knee in subjects with knee OA. Femoral neck bone mineral content (BMC, g) was used in the analysis, whereas femoral neck areal bone mineral density (BMD, g/cm^2) was used during screening of the study participants. Femoral neck cross-sectional area (CSA, [mm^2], the surface area of bone in the cross-section after excluding all trabecular and soft tissue space), and the section modulus (Z, [mm^3], an index of bending strength) were calculated with advanced hip structure analysis (AHA). In K/L 0 group, the average bone trait value of both femoral neck sites was calculated for the analysis.

The root mean square coefficient of variation (CV_{RMS}) for femoral neck BMC measurements with this population was 0.6%. Reproducibility of the DXA measurements was tested from the duplicate measurements of 8 participants within an average 6 (SD 2) days between imaging sessions. The scanner was calibrated daily with bone phantoms (GE Medical System, Lunar Prodigy, Madison WI, USA) for quality assurance.

Knee cartilage assessment

Transverse relaxation time (T2) and dGEMRIC index, i.e., T1 relaxation time in the presence of Gd-DTPA^{2-} were determined using a Siemens Magnetom Symphony Quantum 1.5 T scanner (Siemens AG, Medical Solutions, Erlangen, Germany) with a standard transmit/receive knee array coil. Prior to the measurements, experienced radiologists and technicians were specifically trained to run the MRI research protocol. The participants were imaged lying supine. In the subjects with radiographically-confirmed OA, scans were performed on the side with the higher K/L grade knee, and in the right knee of K/L 0 group. The flexion angle and rotation of the knee was controlled by stabilizing the leg in a fixed position with a leg holder and a custom-made inflatable cushion. T2 mapping, which was performed prior to the dGEMRIC experiment, was carried out using a sagittal multislice, multiecho, fast-spin echo sequence (field of view [FOV] 140 mm, acquisition matrix 256×256, repetition time [TR] 2090 ms, eight echo times [TE] between 13 and 104 ms, echo train length [ETL] 8, 3-mm slice thickness, imaging time=8 min 55 s). The slices were positioned perpendicular to a line tangential to the posterior femoral condyles in the axial scout view. One slice covering the central region of the medial and lateral condyles, were chosen for the analyses. Monoexponential fitting was used to compute relaxation time maps.

For the dGEMRIC imaging, a double dose i.e., 0.4 ml/kg (0.2 mM/kg) intravenous administration of Gd-DTPA^{2-} (Magnevist, Schering, Berlin) was followed by a 90-minute delay with active flexion-extension exercises of the knee for 5 min while sitting, then while walking for 5 min and stair climbing for 5 min in order to enhance the penetration of contrast agent into the knee cartilage. T1 mapping was performed in the sagittal plane using a single slice inversion recovery fast-spin echo sequence (FOV=14 cm, matrix 256×256, TR=1800 ms, TE=13 ms, inversion time TI=50, 100, 200, 400, 800, 1600 ms, echo train length [ETL] 5, 3-mm slice thickness, imaging time per image=6 min 50 s). The slices were positioned perpendicular to a line tangential to the posterior femoral condyles in the axial scout view. The remaining slice was then positioned at the center of the medial and lateral condyles as viewed on the axial scout image.

Full-thickness cartilage regions-of-interest (ROIs) were manually segmented from the most load-bearing areas from single sagittal slices at the center of the medial and lateral femoral and tibial condyles using an in-house MATLAB application (Mathworks, Inc. Natick, MA, USA). The femoral ROI was defined anteriorly at a point opposite the middle of the tibial plateau regarding antero-posterior position, and posteriorly at a point of posterior end of meniscus towards the femoral bone. The tibial ROI was defined anteriorly at a point of meniscus' anterior tip of horn towards the tibial bone, and posteriorly at a point of meniscus' posterior tip of horn towards the tibial bone. Figure 1 shows ROIs from the center of the lateral tibiofemoral compartment. dGEMRIC index is an average T1 spin lattice relaxation time in the presence of Gd-DTPA^{2-} in a given ROI. The dGEMRIC indices were corrected by body mass indices (BMIs) as suggested by Tiderius et al.[19]. On average, the precision (CV_{RMS}) of dGEMRIC in asymptomatic subjects has been shown to be 7% for full-thickness ROIs and 5% for bulk cartilage[20]. The inter-observer error in our laboratory between two independent cartilage investigators (J.M. and E.L., with 6 and 12 years of experience in cartilage analyzing, respectively) was on average 2% for T2 full-thickness ROIs and 3% for dGEMRIC.

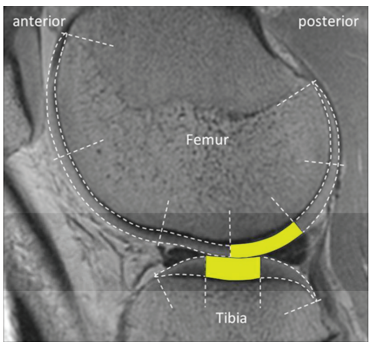

Figure 1. Sagittal T2 image of the segmented and analyzed cartilage regions-of-interest (ROIs) in lateral tibiofemoral compartment. The analyzed ROIs are shown as yellow-colored areas. In the study, the corresponding ROIs were also analyzed from a single sagittal slice in medial tibiofemoral compartment.

Physical function

Agility or dynamic balance was assessed with a standardized figure-of-eight running test of two laps around two poles placed 10 m apart[21]. Maximal isometric knee extension and flexion force was measured in a sitting position with a knee angle of 60° using a dynamometer chair (Good Strength, Metitur Oy, Jyväskylä, Finland)[22]. Leg power was determined by a maximal vertical counter movement jump on a force platform (University of Jyväskylä, Finland)[23]. Cardiorespiratory fitness (estimated oxygen consumption at maximum exertion i.e., VO_{2max}, mL/kg/min) was assessed with a standardized 2-km Walk Test (UKK Institute, Finland)[24].

Questionnaires

Knee pain, stiffness, and self-rated physical functioning were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[25]. General health and leisure time physical activity were assessed by a questionnaire. A health questionnaire addressed medical conditions, current medications and leisure time physical activity, which was converted into metabolic equivalent (MET) hours per week[26].

Variable	K/L 0 (n=12)	K/L 1 (n=25)	K/L 2 (n=53)	P for linearity
Mean age (SD), years	58 (3)	58 (4)	59 (4)	0.52
Mean height (SD), cm	161 (6)	163 (5)	163 (6)	0.64
Mean body mass (SD), kg	67.5 (10.8)	69.9 (9.6)	72.1 (11.3)	0.15
Mean body mass index (SD), kg/m^2	25.8 (3.7)	26.3 (3.1)	27.2 (3.9)	0.16
Mean time from menopause (SD), years	8.3 (5.5)	9.1 (5.9)	9.0 (5.4)	0.81
Current HRT[a] users, n (%)	3 (25)	13 (52)	18 (34)	0.88
Pain killers, n (%)	7 (58)	13 (52)	28 (53)	0.80
Occasional glucosamine use, n (%)	0 (0)	7 (28)	14 (26)	0.15
WOMAC, range 0–100				
Pain	2 (5)	6 (5)	8 (8)	0.008
Stiffness	5 (10)	8 (9)	11 (12)	0.036
Physical function[b]	2 (4)	4 (4)	5 (5)	0.033
Leisure time physical activity, METh/week	18.1 (12.6)	15.6 (7.0)	19.9 (17.8)	0.41
Muscle force, N				
knee extension	381 (49)	384 (79)	417 (82)	0.11[e]
knee flexion	172 (44)	174 (53)	184 (54)	0.55[e]
Power, W	1794 (286)	1888 (375)	1871 (363)	0.97[e]
Dynamic balance[c], s	16.5 (1.7)	17.2 (1.3)	17.2 (2.4)	0.87[e]
VO_{2max}[d], mL/kg/min	29.4 (2.9)	29.4 (2.9)	28.8 (4.5)	0.61[e]

[a]*Hormone replacement therapy.*
[b]*Negative number indicates better physical functioning.*
[c]*Negative number indicates better balance.*
[d]*VO_{2max}, estimated maximal oxygen uptake.*
[e]*Adjusted for age and body mass.*

Table 1. Demographic and clinical characteristics of the study population according to radiographic Kellgren-Lawrence (K/L) grades.

Variable	K/L 0 (n=12)	K/L 1 (n=25)	K/L 2 (n=53)	P for linearity
Bone trait				
Bone mineral content (BMC), g	4.183 (0.836)	4.463 (0.874)	4.726 (0.575)	0.019[a]
Section modulus (Z), mm^3	543 (98)	611 (170)	628 (101)	0.033[a]
Cross sectional area (CSA), mm^2	135 (22)	142 (28)	150 (19)	0.019[a]
T2, ms				
MEDIAL CONDYLE				
Posterior part of central femur	50.4 (2.8)	49.6 (6.3)	50.2 (5.4)	0.85[a]
Central tibia	44.2 (5.2)	44.9 (4.8)	45.1 (4.2)	0.60[a]
LATERAL CONDYLE				
Posterior part of central femur	50.8 (5.4)	50.5 (6.0)	50.4 (5.6)	0.83[a]
Central tibia	38.4 (2.4)	43.5 (6.5)	42.0 (7.3)	0.20[a]
dGEMRIC index, ms				
MEDIAL CONDYLE				
Posterior part of central femur	446 (60)	461 (55)	456 (78)	0.79[b]
Central tibia	362 (67)	412 (72)	402 (58)	0.17[b]
LATERAL CONDYLE				
Posterior part of central femur	474 (67)	512 (75)	469 (59)	0.28[b]
Central tibia	426 (107)	433 (82)	437 (77)	0.63[b]

[a]*Adjusted for age, body mass, and height.*
[b]*Adjusted for age.*

Table 2. Bone and cartilage trait values (mean, SD) from different anatomical regions according to radiographic Kellgren-Lawrence (K/L) grades.

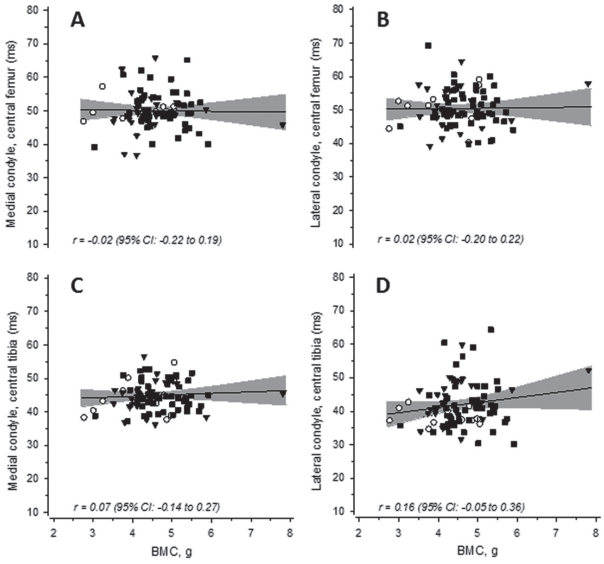

Figure 2. Scatter plots showing the association between the femoral neck bone mineral content (BMC) and knee cartilage T2 relaxation times. Panels in the upper row show the association between BMC and T2 in the posterior part of the central femoral cartilage in both the medial (A) and lateral (B) condyles. Panels in the lower row show the corresponding associations in the central part of the medial (C) and lateral (D) tibial condyles. ○= K/L 0; ▼= K/L 1; ■= K/L 2. The gray band shows the 95% confidence intervals.

Statistical analysis

The results are presented using means, standard deviations (SD) and frequency distributions. Statistical significance for the hypothesis of linearity between radiographic knee OA grades (0 normal, 1 doubtful and 2 minimal) and bone and cartilage characteristics were evaluated by using generalized linear models with appropriate distribution and link function. In addition, the associations of bone and cartilage traits with K/L grading were tested with an effect size, which was calculated using partial Eta-squared (η^2). By convention, values of 0.01, 0.06, and 0.14 are called small, medium, and large effect sizes, respectively[27].The bone traits and cartilage T2 relaxation times were adjusted by age, body mass, and height. The cartilage dGEMRIC indices were adjusted for age. The normality of the variables was tested by using the Shapiro-Wilk W test. All reported p values are two sided, and statistical significance was set at <0.05. Statistical analyses were conducted using Stata v.12.1 (StataCorp, College Station, TX, USA).

Results

Table 1 shows the demographic and clinical characteristics of the subjects according to radiographic K/L grades. There was a linear relationship between perceived knee pain, stiffness, physical functioning, and OA grade, showing that the higher the OA grade was, the more the subjects experienced knee pain (p=0.008 for linearity), stiffness (p=0.036), and physical disability (p=0.033). There were no linear relationships between the OA grade and use of medication, leisure time physical activity, or physical function measures (Table 1).

In the femoral neck, there was a statistically significant linear trend showing that BMC, Z, and CSA increased with higher OA grades (Table 2). The effect sizes indicated that in the bone traits the linear association was at moderate level, i.e. in BMC the η^2 was 0.08, in Z 0.04 and in CSA it was 0.05. The age, body mass, and height-adjusted mean ratio of BMC was 1.10 (95% CI: 1.01 to 1.19), Z was 1.12 (95% CI: 1.02 to 1.21), and CSA was 1.08 (95% CI: 1.01 to 1.16) in the K/L 2 group compared with the K/L 0. The ratios did not differ between the K/L 1 and K/L 0 grades.

In knee cartilage regions, none of the T2 or dGEMRIC indices in the center of the medial or lateral femoral or tibial condyles were linearly related with radiographic grades (Table 2). The effect sizes indicated that in the cartilage traits, the linear associations were considered as not meaningful. There were no relationships between BMC and T2 or dGEMRIC index at any anatomical site (Figures 2 and 3, respectively).

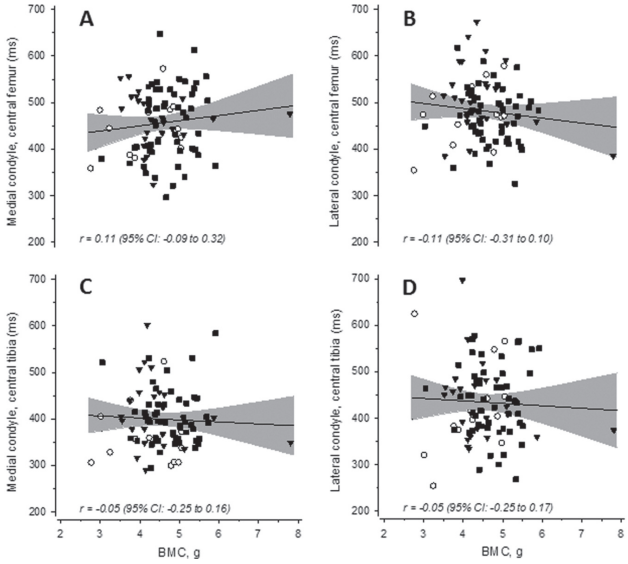

Figure 3. Scatter plots showing the associations between femoral neck bone mineral content (BMC) and knee cartilage dGEMRIC indices. Panels in the upper row show the association between the BMC and dGEMRIC index in the posterior part of the central femoral cartilage in both the medial (A) and lateral (B) condyles. Panels in the lower row show the corresponding associations in the central part of the medial (C) and lateral (D) tibial condyles. ○= K/L 0; ▼= K/L 1; ■= K/L 2. The gray band indicates the 95% confidence intervals.

Discussion

The primary finding of this study was that there was a linear association between femoral neck mineral mass and bending strength, and radiographic grades from K/L 0 to K/L 2. In other words, as the knee OA became radiographically worse the femoral neck bone mineral mass and strength increased. We also found that T2 or dGEMRIC index which reflect the biochemical composition of knee cartilage, was not related to radiographic OA grades. It is also noteworthy that knee pain, stiffness, and physical function disability increased significantly with OA grades, although the symptom values were relatively low even in the highest OA grade (K/L 2).

The bone results of this study are consistent with those of previous large epidemiological surveys showing that radiographic knee OA is associated with high femoral neck bone mineral mass[28-31]. However, so far there are no studies that have simultaneously investigated the relationship between hip bone structure and strength, and estimated biochemical composition of cartilage in mild knee OA. The mechanism whereby OA subjects have more advanced bone structure and strength than non-OA subjects remains unknown. However, Burr & Gallant[32] have suggested that because of the rapid turnover of bone in early OA, the subchondral bone plate and calcified cartilage thickens leading to a subchondral sclerosis while the subchondral trabecular bone may even remain osteopenic. Whether these subchondral bone changes occur at the same time as cartilage deteriorates, and whether these changes occur in more local or general level, is still debatable. Nevertheless, most of the studies in hip and knee OA subjects have demonstrated increased bone mineral mass or density values of different skeletal sites compared with age-matched healthy controls[6,31,33]. In contrast, there are also indications that knee OA is associated with significantly lower BMD values in the affected side compared with the contralateral hip[34], thus, it is important to investigate associations between cartilage and bone at the different sites in same limb.

Our result showing that T2 values were not linearly associated with radiographic OA grades is in accordance with the findings by Koff et al.[35] indicating no association between T2 values and patellar cartilage OA grades. However, our finding is contrary to that of Dunn et al.[36] and Li et al.[37], who showed that regional T2 relaxation times became elongated (high value correspond to compromised cartilage structure degeneration) with higher OA grades. The results of Dunn et al.[36] and Li et al.[37] should be considered with caution, however, due to small sample sizes, and a limited number of echo images used to de-

termine T2 values in the study by Dunn et al.[36]. Similarly, dGEMRIC index showed no association with OA grades. This is in line with the study by Williams et al.[38] who found no relationship between dGEMRIC index and knee OA (K/L grades 1-4) in erosive, narrowed, tibiofemoral joint space compartments. However, when they also analyzed compartments without joint space narrowing, there was a trend toward lower dGEMRIC indices with increasing K/L grades, yet there was significant overlap in dGEMRIC indices between different OA grades. The study was limited by the small sample sizes in different K/L grades.

All in all, the quantitative MRI methodology applied was unable to categorize subjects with mild knee OA according to K/L radiographic criteria. This result could be due to the techniques used (X-ray and qMRI) that focus on different tissue types. In OA, both osteophyte formation and increased bone mineral mass are features of bone, which were measured using the same methodology derived from increased attenuation of X-rays in bone mineral mass. Thus, these bone hypertrophy forms can be expected to be associated with each other. However, the qMRI methods are surrogates for cartilage matrix constituents, indicating cartilage biology beyond radiographic detection. Moreover, the cartilage compositional changes most likely precede changes in bone and cartilage quantity in early OA. Furthermore, there are conflicting results about the cartilage GAG content changes in early OA[39]. GAG content may increase[40,41] or diminish[42,43] in early OA. For instance, in a recent study Stubendorff et al.[44] suggested that dGEMRIC-derived sulphated glycosaminoglycan (sGAG) content may remain at rather constant levels in early hip OA due to compensative sGAG synthesis. This might explain our findings why there were no linear associations between dGEMRIC indices and radiographic knee OA grades, or between dGEMRIC indices and femoral neck BMC. An anomalous behavior of cartilage GAG content may reflect a more complex pattern of early OA progression than anticipated. Alternatively, dGEMRIC may not be a specific method for detecting early cartilage degeneration. On the other hand, previous cross-sectional studies reported differences in dGEMRIC indices between asymptomatic versus OA knees[45], and arthroscopically normal femoral compartments versus diseased compartments[46]. Nonetheless, our qMRI results challenge the role of radiographic evaluation of OA, since articular cartilage has an important role in OA development and is not adequately addressed using K/L scoring.

The strength of the present study is that, to our knowledge, it is the first to simultaneously investigate the relationship between bone mineral mass and OA by detecting bone structural characteristics and articular cartilage measures. In previous knee OA and OP relationship studies, which were published largely in the 1990s[28-31], the biochemical composition of knee cartilage was not taken into account mainly because appropriate *in vivo* cartilage imaging techniques were not available. Additionally, recent cross-sectional studies using standard MRI techniques have focused on delineating cartilage morphology[9,10] rather than the biochemical composition of cartilage. Standard MRI sequences, however, cannot detect the initial stages of OA, including glycosaminoglycan loss, increased water content, and disorganization of the collagen network[47].

The present study has some limitations. Only one radiologist graded knee OA according the K/L scoring system; however, it is unlikely that two radiologists would have improved the grading reliability as we had a musculoskeletal radiologist with 20 years of experience. The study was also limited because bone traits in the hips and cartilage traits in the knees according to radiographic knee OA were not obtained of the same body part. This cannot though be considered as a crucial failure due to systemic disease component of both OP and OA. The participants' history of development of knee OA was not available. In addition, we had a rather select group of study participants with K/L grades 1 and 2 because of the related exercise intervention study[17], and a relatively small sample size in the K/L grade 0 group. To investigate this aspect, further investigations including subjects across a radiographic spectrum of OA are required with prospective longitudinal follow-ups.

In conclusion, this study demonstrated that femoral neck structure, strength and mineral mass were inversely related to mild knee OA in postmenopausal women, i.e. the femoral neck rigidity improvement was associated with severity of radiographic knee OA. These results have implications for the hypothesis that there is an inverse relationship between OA and OP. However, with this population there was no association between radiographic OA grades and knee cartilage biochemical composition assessed using quantitative MRI measures; T2 relaxation time and dGEMRIC. The reason for this inconsistent periarticular cartilage-bone interaction remains unclear, but the radiographic K/L scoring system may not be sensitive to cartilage changes in early to mid-stage knee OA.

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III

EFFECTS OF HIGH-IMPACT TRAINING ON BONE AND ARTICULAR CARTILAGE: 12 MONTH RANDOMIZED CONTROLLED QUANTITATIVE MRI STUDY

by

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Effects of High-Impact Training on Bone and Articular Cartilage: 12 Months Randomized Controlled Quantitative Magnetic Resonance Imaging Study

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Additional Supporting Information may be found in the online version of this article.

ABSTRACT

Osteoarthritis and osteoporosis often coexist in postmenopausal women. The simultaneous effect of bone-favorable high-impact training on these diseases is not well understood and is a topic of controversy. We evaluated the effects of high-impact exercise on bone mineral content (BMC) and the estimated biochemical composition of knee cartilage in postmenopausal women with mild knee osteoarthritis. Eighty women aged 50-66 years with mild knee osteoarthritis were randomly assigned to undergo supervised progressive exercise 3 times a week for 12 months (n=40) or to a non-intervention control group (n=40). BMC of the femoral neck, trochanter and lumbar spine was measured by dual-energy X-ray absorptiometry (DXA). The biochemical composition of cartilage was estimated using delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), sensitive to cartilage glycosaminoglycan content, and T2 mapping that is sensitive to the properties of the collagen network. In addition, clinically important symptoms and as physical performance related risk factors of falling; dynamic balance, maximal isometric knee extension and flexion forces, leg power and cardiorespiratory fitness were evaluated. Thirty-six trainees and 40 controls completed the study. The mean gain in femoral neck BMC in the exercise group was 0.6% (95% CI: -0.2 to 1.4) and the mean loss in the control group was -1.2% (95% CI: -2.1 to -0.4). The baseline, body mass and body mass change adjusted BMC change between the groups was significant (P=0.005), while no changes occurred in the biochemical composition of the cartilage, as investigated by MRI. Balance, muscle force and cardiorespiratory fitness improved significantly more (3-11%) in the exercise group than in the control group. Progressively implemented high-impact training, which increased bone mass, did not affect the biochemical composition of cartilage and may be feasible in the prevention of osteoporosis and physical performance related risk factors of falling in postmenopausal women.

KEY WORDS: EXERCISE; OSTEOARTHRITIS; OSTEOPOROSIS; MENOPAUSE; RADIOLOGY

INTRODUCTION

Osteoarthritis (OA) and osteoporosis (OP) are age related diseases that frequently coexist in postmenopausal women.[1] Exercise is widely recommended as one of the key preventive strategies to reduce the risk of OP, falls and fractures,[2,3] and also as a non-pharmacologic treatment for mild to moderate knee OA.[4,5] High-impact exercise loading with versatile movements have been shown to have the most beneficial osteogenic effect while cardiorespiratory fitness exercise and resistance training have been shown to be beneficial in reducing pain and improving physical function in OA.[6] However, as far as we know, only one rather short and small randomized controlled exercise intervention study has been published in the quest for understanding cartilage adaptation to exercise in patients at risk of OA.[7] By applying the delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) technique,[8] investigators suggested that adult human cartilage has the potential for exercise adaptation by increasing cartilage glycosaminoglycan (GAG) content.[7] Although the aforementioned study indicated a positive effect of exercise on articular cartilage, high intensity loading and sports participation have been associated with joint injury and OA development.[9,10] Thus, what is controversial and poorly understood, is the impact of exercise simultaneously on bone and cartilage. Therefore, the purpose of this study was to discover the effects of a 12-month high-impact exercise program in postmenopausal women with mild knee OA on bone mineral content (BMC) and knee cartilage indices using dGEMRIC and T2 relaxation time mapping.

MATERIALS AND METHODS

Design and participants

This study was a 12-month randomized controlled trial (ISRCTN58314639) with two experimental arms. The trial profile is shown in Figure 1. The voluntary participants from the Jyväskylä region in Central Finland (n=298) were recruited through a local newspaper advertisement. After eligibility was assessed by telephone interview, screening radiographs taken from tibiofemoral joints, DXA and clinical examinations obtained, 80 subjects met the inclusion criteria. Measurements were made at baseline and after the 12-month intervention. All outcome assessors, except JM in knee cartilage segmentation, were blinded to the treatment-group assignment. The criteria for eligibility were: postmenopausal women, age 50–65 years, knee pain on most days, regular intensive exercise no more than twice a week, no illnesses that contraindicated exercise or would limit participation in the exercise program and a Kellgren/Lawrence (K/L) radiographic grading of tibiofemoral joint OA 1-2. The criteria for exclusion were: T-score for femoral neck bone mineral density (BMD, g/cm^2) lower than -2.5 (*i.e.,* indicating osteoporosis), body mass index (BMI) ≥ 35 kg/m^2, knee instability or surgery of the knee due to trauma, inflammatory joint disease, intra-articular steroid injections in the knee during the preceding 12 months, contraindications to MRI, allergies to contrast agents or renal insufficiency.

Each participant was randomly allocated by the statistician blinded for the study participants to the exercise group (n=40) or the control group (n=40) according to a computer generated, blocked randomisation list. We used a block size of ten, stratified according to K/L grade 1 and 2.

The study protocol was approved by the Ethics Committee of the Central Finland Health Care District (Dnro1E/2008). The protocol conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Radiographic screening

The radiographs were acquired in the screening examinations with a postero-anterior view of the tibiofemoral joint in a semiflexed weight bearing position. A tibiofemoral joint OA severity of grade 1 (possible osteophytes) or 2 (definite osteophytes, possible joint space narrowing) were determined according the K/L classification.[11]

Medical screening

A structured general medical examination with detailed structured examination of the knees was performed by the attending physician to ensure that the participants would not have any limitation on study participation.

Questionnaire

General health and habitual physical activity were assessed with a questionnaire at baseline. A health questionnaire addressed medical conditions, current medications, anamnestic records of gynaecology and knee OA, and current physical activity in leisure time. The habitual physical activity was converted into MET-hours per week.[12]

Bone scanning

Bone mineral content of the femoral neck and trochanter from the higher K/L grade knee side and lumbar spine (L2-L4) were measured with dual-energy X-ray absorptiometry (DXA, GE Medical Systems, Lunar Prodigy, Madison, WI, USA) as an outcome measure.[13] In addition, BMD of the lumbar spine and both femoral necks were measured and used for screening the study participants. In our laboratory the root-mean-square average coefficient of variation (CV_{RMS}) for DXA

measurement was 0.6% for femoral neck BMC and 1.0% for the spine region L2-L4 within an average of 6 (SD 2) days between imaging sessions for 8 participants.

Cartilage measures

The dGEMRIC index, *i.e.,* T1 relaxation time in the presence of Gd-DTPA^{2-} and T2 relaxation time (T2)[14,15] were determined using a Siemens Magnetom Symphony Quantum 1.5 T scanner (Siemens AG, Medical Solutions, Erlangen, Germany) with a standard transmit/receive knee array coil. For dGEMRIC measurements, an intravenous administration of 0.4 ml/kg (double dose) of Gd-DTPA^{2-} (Magnevist, Schering, Berlin) was followed by active knee flexion-extension exercises for 5 min while sitting, then 5 min walking and 5 min stair climbing. After a 90-minute delay from injection T1 relaxation time measurements were performed. T2 relaxation time measurements were performed prior to contrast agent administration (more detailed MRI protocol is provided in Additional Supporting Information).

Weight bearing cartilage regions of interest (ROIs) from single sagittal slices at the centre of the medial and lateral tibial and femoral condyles were manually segmented using an in-house MATLAB application (Mathworks, Inc. Natick, MA, USA) (Figure 2). dGEMRIC indices were corrected for BMI.[16] Previously, we have shown that the precision (CV_{RMS}) of dGEMRIC in asymptomatic subjects as repeated three times with an average interval of 5 (SD 3) days between scans is on average 7% for full-thickness ROIs and 5% for bulk cartilage.[14] In our laboratory, the inter-observer error (CV_{RMS}) for T2 full-thickness ROIs was on average 2% and 3% for dGEMRIC.

Physical function

Dynamic balance was assessed with a standardized figure-of-eight running test of two laps around two poles placed 10 m apart.[17,18] Maximal isometric knee extension and flexion force was measured in a sitting position with a knee angle of 60° using a dynamometer chair (Good Strength, Metitur Oy, Jyväskylä, Finland).[19] Leg power was determined by a maximal vertical counter movement jump on a force platform (University of Jyväskylä, Finland).[20] Cardiorespiratory fitness (VO_2max, ml/kg/min) was assessed with a standardized 2-km Walk Test (UKK Institute, Finland).[21]

Clinically important symptoms

Perceived pain, stiffness, and self-rated physical functioning were assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[22] We used a visual analogue scale (VAS) format, where higher scores on VAS indicate higher degree of joint pain, joint stiffness and functional limitation.

Exercise protocol

High-impact type multidirectional a) aerobic and b) step-aerobic jumping exercise programs alternated every two weeks. Supervised group exercise classes lasting 55 minutes, were carried out three times a week for 12 months. The loading was gradually increased after three months by progressively raising the height of the foam fences from 5 to 20 cm in aerobic exercises, and the height of the step benches from 10 to 20 cm in jumping exercises (more detailed exercise protocol is provided in Additional Supporting Information).[17,18,23]

Assessment of exercise loading. The high-impact exercise was quantified by recording the number and intensity of acceleration peaks (impacts) with accelerometers (Newtest, Oulu, Finland) during one exercise session in each of the 3-month exercise periods. The number of impacts were

combined to four acceleration levels; low (0.3-2.4 g), moderate (2.5-3.8 g), high (3.9-5.3 g) and very high (5.4-9.8 g), where g=9.81 $m \cdot s^{-2}$, 0 g equated to standing still.[24] The maximum heart rate values were collected with monitors (Polar F6, Polar Electro Oy, Kempele, Finland) and the rate of perceived exertion (RPE) using the Borg scale (6 to 20).[25]

Control group

The controls were asked to maintain their usual activities and they were offered the possibility of participating in a social group meeting every third month.

Daily physical activity

The number and intensity of acceleration peaks (impacts) due to daily physical activities from all participants (intervention training classes not included) were recorded semi-annually at four and ten months for three consecutive days using an accelerometer (Newtest, Oulu, Finland). The gathered data were converted into a Daily Impact Score (DIS_{Log}).[26]

Statistical analysis

All analyses were based on intention-to-treat principles. Results were expressed as means with standard deviation (SD) and as medians with interquartile range (IQR). Statistical comparison between groups was made by the Chi-Square or Fisher's exact test and t-test. Statistical comparison of changes in outcome measurements was performed by using paired t-tests or analysis of covariance (ANCOVA). Quantitative MRI was analysed by the bootstrap type Hotelling T-squared test (MANOVA); because of the violation of distributions assumptions. The Hotelling T-squared test is a method of comparing means of all variables of interest simultaneously, while maintaining the chosen magnitude of Type I error. Holm's procedure was used to adjust for multiple comparisons and to identify significant differences in at least one of the 8 cartilage ROIs between-

group MANOVA comparisons. Thus the confidence intervals (95% CI) for MRI outcome means were obtained by bias corrected bootstrapping (5000 replications).The group differences for BMC, MRI, physical function and clinical symptom outcomes were adjusted for baseline values, and in addition, BMC was adjusted by body mass and body mass change. Correlation coefficients were calculated by the Pearson method. Statistical analyses were performed using statistical software (Stata, release 12.1, StataCorp, College Station, Texas).

Preceding the study, the intended sample size for power calculation was based on the primary hypothesis. A sample size of 70 subjects (35 in each group) was required to detect differences in change between the intervention and the control groups of 0.08 grams (~2%) in the femoral neck BMC (α=0.05, power=80%), considering a drop-out rate of approximately 10%. For dGEMRIC and T2 we could not reliably calculate the intended sample sizes, because previous long-term exercise interventions for cartilage change do not exist.

RESULTS

Baseline characteristics are given in Table 1. During the intervention the change of the mean body mass in the exercise group was -1.5 kg (95% CI: -2.5 to -0.4) and in the control group 0.5 kg (-0.6 to 1.5).

Program feasibility

Immediately after randomization, two trainees withdrew and two others discontinued their participation from the exercise group at weeks 3 and 5, whilst none were lost in the control group. There were six medical consultations due to musculoskeletal injuries or other symptoms; 1) knee swelling, 2) distension of the hamstring muscles, 3) ankle sprain, 4) low-back pain, 5) Achilles tendon pain and 6) asthma-like symptoms during exercise classes. Training break was used as a treatment in these cases. All these trainees returned to the exercise regime within 5 to 21 days. At the 10th week one trainee had a pelvic fracture in a traffic accident. She recovered fully and returned to the training sessions after eleven weeks cessation. Another trainee terminated the exercise at the 36th week due to progression of neurological symptoms. Mean training compliance was 68% and the mean training frequency was 2.1 (SD 0.9) per week (with lost trainees included). The average rate of perceived exertion (RPE) of the exercise program was 13.9 (0.5). In the control group there were two visits to the attending physician due to previous meniscal tear injury and cardiac dysrhythmia. The number of visits to the attending physician did not differ statistically between the groups (P=0.15).

Exercise loading

The mean number of acceleration peaks during one training session was 2114 (SD 359) at low, 76 (5) at moderate, 41 (7) at high, and 44 (16) at very high acceleration levels. The mean exercise induced maximum heart rate value was 148 (SD 6).

Daily physical activity

The mean Daily Impact Score (DIS_{Log}) outside intervention sessions was 163 (43) in the exercise group (n=34) and 168 (46) in the control group (n=40) (P=0.64). The most common physical activity modes were walking, biking and Nordic walking in both groups.

Bone measurements

The baseline values and the treatment effect of BMC are given in Table 2. After 12 months, BMC at the femoral neck was significantly greater (1.6%) in the exercise group than the control group (Figure 3). There were no significant inter-group differences in the trochanter or lumbar spine (Table 2, Figure 3). There was no relationship between femoral neck BMC change and the training compliance (data not shown).

Cartilage measurements

The baseline values and the treatment effect of the dGEMRIC index and T2 for different ROIs are given in Table 3. After 12 months, there were no significant changes between the groups at any dGEMRIC index or T2 after corrected multiple comparisons. Within the groups all dGEMRIC index and T2 effect sizes were less than 0.5 (Figure 4).

There were no relationships between changes of the femoral neck BMC and changes in dGEMRIC index segments in the medial (r=0.03; 95% CI: -0.14 to 0.20) or lateral condyles (r=-0.07: -0.29 to 0.16) of the posterior central femur, or in the medial (r=-0.02; -0.19 to 0.16) or lateral condyles (r=0.14; -0.08 to 0.35) of central tibial cartilage.

Physical function, perceived pain, knee stiffness and self-rated physical functioning

The exercise group improved their isometric leg extension force by 11% (P=0.009), dynamic balance by 3% (P=0.022) and cardiorespiratory fitness by 4% (P=0.027) when compared to the control group (Table 4). There were no inter-group differences in knee pain, stiffness or self-rated physical functioning (Table 4).

DISCUSSION

This 12-month randomized, controlled high-impact exercise trial in postmenopausal women with mild knee OA (K/L 1-2) showed a significant increase in femoral neck BMC. The exercise was also able to favourably modify physical function, *i.e.,* to lower multiple fall risk factors for osteoporotic fractures among postmenopausal women. The progressively implemented high-impact jumping exercise did not have negative or positive effects on knee cartilage biochemical composition assessed using quantitative MRI measures, the dGEMRIC index and T2 (in dGEMRIC, high values correspond to high GAG content, and in T2 high values correspond to compromised cartilage structure degeneration). In addition, the training was well tolerated; it did not induce knee pain, the general training compliance was high and there were only a few dropouts. These results suggest that bone-favourable exercise can be recommended for postmenopausal women with early OA, who may be at risk of OP.

Regular and sufficient bone loading is vital for bone health, and high-impact loading is undoubtedly the most osteogenic activity to undertake.[27] In the present study we found an osteogenic effect on femoral neck BMC in postmenopausal women, which is consistent with a previous systematic review.[28] We did not find any effect of high-impact exercise on bone mineral mass of the lumbar spine in contrast to some studies showing a positive response to exercise at the lumbar spine among elderly women.[28,29] However, our previous findings are more consistent with the current results, indicating no such impact exercise effect on lumbar spine BMC.[17,18] The somewhat different group characteristics, exercise protocols and exercise adherence between the studies may at least partly explain the inconsistent results. In addition to the present osteogenic effect on femoral neck BMC in postmenopausal women, we showed other positive effects of high-impact training on fall risk factors such as balance, lower limb muscle force and cardiorespiratory fitness. These results are

also in line with the previous high-impact intervention studies in postmenopausal and elderly women,[17,18,30,31] and they showed that this study program is suitable for fall prevention strategies.

Previously, the high-impact jumping exercise loading, that is, a fast loading rate of 2-6 times body mass was shown to be osteogenic.[23] In addition, the osteogenic acceleration threshold for hip BMD has been shown to be 3.9 g in premenopausal women.[32] In the present study, acceleration peaks higher than 3.9 g (which corresponds to 4.9 times body mass) were exceeded with an average of 85 impacts in training classes, thus representing the true osteogenic nature of the present exercise program. This is in line with a previous animal study, reporting that skeletal adaptation is mainly dependent of strain rate (fast loading rate) and only between 4 and 36 loading cycles is needed daily.[33] For comparison, knee implant compressive forces ranging from 2.2 to 3.5 times body mass have been measured for activities of daily living[34] and the peak tibiofemoral compressive force has been reported to be 10.4 times body weight when running.[35] After all, even though the exercise loading seemed occasionally rather high in our study, the total number of impacts was at a reasonable level, and thus loading remained in the physiological “safe loading range” in terms of cartilage health.

Bone adapts to loading by adjusting its mass, architecture and structural strength.[36,37] On the contrary, cartilage has only a very limited ability to undergo long-term volume changes,[38,39] but its biochemical composition can adjust.[40,41] However, in our study, we did not find any changes in the estimated biochemical composition of cartilage, which is dissimilar to the findings of a study by Roos and Dahlberg.[7] Their study showed significant positive change in the mean dGEMRIC index after a moderate 4-month weight bearing exercise program in meniscectomised middle-aged subjects. These two studies differ most probably in the age of participants and in the pathophysiological condition of knee cartilage. Moreover, the exercise loading modalities may

explain different cartilage responses. Van Ginckel *et al.* showed that dGEMRIC indices in young novice female runners with asymptomatic knees were higher after a 10-week running training program than in the control group.[42]

The most important finding was that bone strengthening high-impact jumping exercise, which also had positive effects on physical performance related risk factors of falling, was not harmful for the integrity of articular cartilage in mild knee OA. While the exercise group had more physician consultations due to exercise-related musculoskeletal symptoms than the control group, the symptoms were temporary and all trainees were able to return to their exercise without further complications. Thus, if an osteogenic bone response is desired, bone favorable exercises can be incorporated into an OA patient's exercise program. However, high-impact exercise may not provide the optimal loading modality for patients with knee OA. Further, these study findings apply to normal or somewhat overweight postmenopausal women with mild knee OA only and cannot be generalized to older people, obese people, or those with more severe knee joint conditions or to men who tend to jump more vigorously. Thus, further RCTs including subjects from both sexes with different anthropometric measures and OA grading are needed. Moreover, future studies should evaluate whether low-impact or non-impact loading modalities, such as cycling or aquatic training have beneficial effects on articular cartilage and may reduce risk factors of falling.

This study has several strengths. Firstly, this is the first long-term trial with high training compliance assessing the effect of high-impact exercise on articular cartilage using both dGEMRIC and T2 mapping in subjects with mild knee OA. Secondly, there were only a few dropouts because the training was well tolerated, and also because of an observed engaging team spirit. Thirdly, we were able to quantify the impact loading of exercise by using accelerometers. Fourthly, the study design fulfilled all the important quality criteria of a randomized controlled trial except for blinding

of the participants in exercise therapy, which is quite natural in exercise therapy studies.[43] The study was limited by single slice MRI data from the load bearing area of each condyle, however, it is unlikely that three-dimensional MRI sequences would have revealed a difference between the exercise groups as load bearing cartilage was evaluated from the MRI images. Furthermore, occasionally thinned or deteriorated cartilage prevented reliable segmentation of cartilage into superficial and deep layers, which might have provided more information about exercise induced focal cartilage alterations. Nonetheless, the previous clinical studies have clearly demonstrated the relationship between dGEMRIC index measured in full-thickness cartilage and early signs of OA reflecting the biochemical differentiation of disease.[44,45]

In summary, progressively implemented high-impact training, which increased bone mass and physical function, did not have effects on the biochemical composition of cartilage and may be feasible in the prevention of OP and physical performance related risk factors of falling in postmenopausal women.

DISCLOSURES

Riikka Ahola and Timo Jämsä are inventors of patent application FI 20090320. All other authors state that they have no conflict of interest.

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Authors' roles: Study design: AHeinonen, AHäkkinen, IK, MTN, TJ, and JM. Study conduct: JM, EL, RO, and HS. Data collection: JM and RA. Data analysis: HK, AHeinonen, and JM. Data interpretation: AHeinonen, MTN, JM, HK, EL, AHÄkkinen, UMK, and IK. Drafting manuscript: JM, AHeinonen, and AHäkkinen. Revising manuscript content: JM, AHeinonen, AHäkkinen, UMK, IK, MTN, EL, TJ, HK, RA, RO, and HS. Approving final version of manuscript: JM, AHeinonen, AHäkkinen, UMK, IK, MTN, EL, TJ, HK, RA, RO, and HS. AHeinonen and JM takes responsibility for the integrity of the data analyses.

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Figure legends:

Figure 1. Flowchart of the recruitment process and inclusion of participants.

Figure 2. Illustration of the regions of interest (ROIs) in the weight bearing full-thickness femoral and tibial cartilage. The ROIs are marked with white coloured areas in a single sagittal slice from the center of the lateral femoral condyle. In the study, the corresponding ROIs were also segmented and analyzed from the single sagittal slice from the center of the medial femoral condyle. Nomenclature for abbreviated segments: aCF = anterior central femur, pCF = posterior central femur, aPF = anterior part of posterior femur, aT = anterior tibia, cT = central tibia, pT = posterior tibia.

Figure 3. The percent change with 95% confidence intervals in the femoral neck, trochanter and lumbar spine L2-L4 bone mineral content (BMC) in the exercise group and the control group.

Figure 4. Effect sizes at different cartilage region of interests (ROIs) from medial and lateral knee condyles. Medium (0.50) effect sizes are illustrated with dotted lines. Nomenclature for abbreviated segments: aCF = anterior central femur, pCF = posterior central femur, aPF = anterior part of posterior femur, aT = anterior tibia, cT = central tibia, pT = posterior tibia.

Table 1. Baseline Demographic and Clinical Characteristics of the Participants

	Exercise group (n=38)	Control group (n=40)
Age (years)	58 (4)	59 (4)
Height (cm)	165 (6)	161 (5)
Body mass (kg)	73.4 (9.4)	69.4 (11.7)
Body mass index (kg/m^2)	27.1 (3.1)	26.7 (4.2)
Occupational status, n (%)		
Employed	26 (68)	19 (48)
Unemployed	4 (11)	6 (15)
Retired	8 (21)	15 (37)
Time from menopause (years)	9 (6)	9 (5)
Hormone replacement therapy[a], n (%)	19 (50)	12 (30)
Dietary supplements		
Calcium intake, n (%)	15 (39)	19 (47)
Dose, median (IQR), mg/day	*500 (500 , 500)*	*500 (500 , 500)*
D-vitamin intake, n (%)	19 (50)	16 (41)
Dose, median (IQR), µg/day	*10 (5, 10)*	*10 (9, 12)*
Pain killers, n (%) of users	24 (63)	17 (42)
Glucosamine use occasionally, n (%)	8 (21)	13 (32)
Kellgren Lawrence grade, n (%)		
Grade 1	12 (32)	13 (32)
Grade 2	26 (68)	27 (68)
Knee pain during last week[b] (mm)	10 (13)	10 (13)
Habitual physical activity (METh/week)	18.1 (13.1)	18.9 (17.2)

Values are means (SD) or n (%) unless otherwise noted.

IQR = interquartile range.

[a]previous or current users.

[b]range: 0-100 mm.

Table 2. Baseline, change and treatment values of bone mineral content in the femoral neck (FN), trochanter (TROC) and lumbar spine (L2-L4)

	Baseline, Mean (SD)		Change to Month 12, Mean (95% CI)		Treatment effect	P-values		
	Exercise	Control	Exercise	Control	Mean (95% CI)	Crude	Adjusted[a]	Adjusted[b]
FN	4.80 (0.76)	4.50 (0.62)	0.03 (-0.01 to 0.07)	-0.06 (-0.10 to -0.02)	0.09 (0.03 to 0.14)	0.002	<0.001	0.005
TROC	11.40 (2.19)	11.57 (2.33)	0.12 (-0.07 to 0.30)	-0.01 (-0.20 to 0.17)	0.13 (-0.12 to 0.39)	0.31	0.41	0.54
L2-L4	53.00 (9.04)	51.81 (9.23)	0.26 (-0.50 to 1.02)	-0.63 (-1.21 to -0.05)	0.90 (-0.04 to 1.82)	0.060	0.086	0.11

CI = confidence interval.

[a]adjusted by baseline values and body mass.

[b]adjusted by baseline values and body mass change.

Table 3. Baseline, change and treatment values of dGEMRIC index and T2 from different full-thickness cartilage regions of interest. In dGEMRIC, high values correspond to high glycosaminoglycan content, and in T2 high values correspond to compromised cartilage structure degeneration.

	Baseline, Mean (SD)		Change to Month 12, Mean (95% CI)		Treatment effect	P-value[a]	
	Exercise (n=36)	Control (n=40)	Exercise (n=36)	Control (n=40)	Mean (95% CI)	Crude	Adjusted
FEMUR: Medial condyle							
dGEMRIC							
anterior Central	426 (64)	452 (60)	-5 (-32 to 22)	-15 (-42 to 10)	9.1 (-28.0 to 46.2)		
posterior Central	442 (73)	470 (69)	0 (-25 to 19)	-10 (-29 to 7)	9.3 (-20.0 to 38.6)		
anterior Posterior[b]	477 (63)	479 (69)	16 (-10 to 41)	-7 (-30 to 17)	22.8 (-10.5 to 56.1)		
entire related area						0.61	0.46
T2							
anterior Central	49.0 (4.3)	48.5 (6.6)	0.3 (-1.5 to 1.9)	-0.9 (-2.6 to 0.9)	1.18 (-1.33 to 3.70)		
posterior Central	50.8 (6.0)	49.3 (5.5)	0.9 (-0.4 to 2.1)	-0.5 (-1.6 to 0.7)	1.37 (-0.34 to 3.09)		
anterior Posterior[b]	53.1 (3.7)	52.2 (4.6)	-0.2 (-1.2 to 0.7)	-0.7 (-2.1 to 0.4)	0.51 (-1.06 to 2.08)		
entire related area						0.46	0.31
TIBIA: Medial condyle							
dGEMRIC							
Anterior	394 (66)	415 (63)	13 (-14 to 39)	12 (-21 to 44)	0.3 (-42.2 to 42.9)		
Central	394 (63)	413 (61)	10 (-21 to 42)	13 (-24 to 51)	-3.2 (-52.3 to 45.8)		
Posterior	412 (65)	429 (48)	1 (-31 to 31)	20 (-6 to 44)	-19.1 (-59.7 to 21.6)		

entire related area						0.52	0.045[c]
T2							
Anterior	43.4 (3.5)	43.7 (3.1)	-0.1 (-1.2 to 1.0)	0.7 (-0.4 to 1.6)	-0.76 (-2.23 to 0.71)		
Central	45.0 (4.9)	45.0 (3.9)	1.5 (0.0 to 3.4)	-0.0 (-1.2 to 1.3)	1.50 (-0.57 to 3.56)		
Posterior	44.4 (3.6)	44.8 (3.6)	0.4 (-0.8 to 1.4)	0.3 (-0.8 to 1.4)	0.03 (-1.54 to 1.59)		
entire related area						0.32	0.26
FEMUR: Lateral condyle							
dGEMRIC							
anterior Central	437 (55)	441 (54)	4 (-16 to 23)	14 (-8 to 36)	-9.3 (-38.1 to 19.6)		
posterior Central	483 (77)	479 (58)	-12 (-39 to 11)	6 (-10 to 23)	-18.0 (-47.2 to 11.2)		
anterior Posterior[b]	449 (79)	470 (65)	15 (-11 to 43)	-5 (-27 to 15)	20.4 (-13.9 to 54.7)		
entire related area						0.24	0.35
T2							
anterior Central	48.8 (6.4)	49.1 (5.8)	0.5 (-1.4 to 2.4)	-0.1 (-1.7 to 1.4)	0.56 (-1.96 to 3.09)		
posterior Central	50.1 (6.0)	50.9 (5.3)	0.7 (-0.9 to 2.7)	1.0 (-0.2 to 2.2)	-0.38 (-2.53 to 1.76)		
anterior Posterior[b]	49.7 (4.7)	49.9 (4.6)	0.3 (-1.2 to 2.2)	0.2 (-0.8 to 1.2)	0.15 (-1.84 to 2.14)		
entire related area						0.87	0.85
TIBIA: Lateral condyle							
dGEMRIC							
Anterior	415 (68)	440 (65)	14 (-13 to 38)	-10 (-37 to 16)	23.8 (-13.5 to 61.2)		

Central	427(83)	445 (74)	14 (-10 to 39)	-7 (-38 to 26)	20.4 (-19.3 to 60.1)		
Posterior	424 (64)	425 (60)	-2 (-24 to 20)	2 (-23 to 29)	-4.2 (-37.3 to 29.0)		
entire related area						0.27	0.75
T2							
Anterior	42.5 (3.9)	42.3 (4.7)	-0.1 (-1.5 to 1.4)	0.8 (-0.7 to 2.1)	-0.89 (-2.94 to 1.16)		
Central	42.7 (8.0)	42.3 (6.2)	0.0 (-1.6 to 1.6)	0.5 (-1.0 to 2.0)	-0.42 (-2.63 to 1.78)		
Posterior	44.6 (3.9)	45.5 (4.8)	-0.6 (-2.0 to 1.0)	0.2 (-1.0 to 1.6)	-0.83 (-2.74 to 1.09)		
entire related area						0.69	0.59

CI = confidence interval.

[a] bootstrap type MANOVA for related samples in 3 areas of the same load-bearing cartilage simultaneously; crude and adjusted baseline values.

[b]anterior part of posterior femoral cartilage.

[c]significance level at P=0.36 after multiple correction.

Table 4. Baseline, change and treatment values of the clinical outcomes of Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and physical function measures.

	Baseline, Mean (SD)		Change to Month 12, Mean (95% CI)		Treatment effect	P-value	
	Exercise (n=36)	Control (n=40)	Exercise (n=36)	Control (n=40)	Mean (95% CI)	Crude	Adjusted[a]
WOMAC (0 to 100 scale)							
Pain	8 (8)	6 (6)	-2 (-6 to 3)	0 (-2 to 3)	-2 (-7 to 2)	0.31	0.47
Stiffness	10 (13)	9 (9)	-4 (-9 to 1)	0 (-4 to 5)	-3 (-11 to 3)	0.29	0.29
Physical functioning[b]	5 (5)	4 (4)	-1 (-3 to 1)	1 (0 to 3)	-2 (-5 to 1)	0.12	0.12
PHYSICAL FUNCTION							
Dynamic balance[c], s	16.9 (1.5)	17.4 (2.7)	-0.6 (-0.9 to -0.4)	-0.2 (-0.5 to -0.2)	-0.5 (-0.9 to -0.1)	0.02	0.003
Knee extension force[d], N	401 (95)	414 (70)	21 (-1 to 44)	-14 (-29 to 1)	35 (9 to 61)	0.009	0.006
Knee flexion force[d], N	183 (58)	179 (51)	8 (-6 to 22)	15 (3 to 27)	-7 (-25 to 11)	0.44	0.45
Leg extension power, W	1974 (381)	1805 (341)	47 (-7 to 102)	21 (-30 to 72)	26 (-47 to 100)	0.48	0.22
VO_{2max}[e], ml ·/kg/min	29.3 (3.3)	29.2 (4.2)	1.4 (0.7 to 2.5)	0.3 (-0.4 to 1.0)	1.1 (0.1 to 2.1)	0.03	0.03

CI= confidence interval.

[a]adjusted by baseline values.

[b]negative number indicates improved physical functioning.

[c]negative number indicates improved balance.

[d]average of both legs best attempt.

[e]VO_{2max}, estimated maximal oxygen uptake.

IV

EFFECT OF PROGRESSIVE HIGH-IMPACT EXERCISE ON FEMORAL NECK STRUCTURAL STRENGTH IN POSTMENOPAUSAL WOMEN WITH MILD KNEE OSTEOARTHRITIS: A 12-MONTH RCT

by

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Effect of Progressive High-Impact Exercise on Femoral Neck Structural Strength in Postmenopausal Women with Mild Knee Osteoarthritis: A 12-Month RCT

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(Additional Supporting Information may be found in the online version of this article)

DISCLOSURES

RA and TJ are inventors of patent application FI 20090320. All other authors state that they have no conflicts of interest.

ABSTRACT

It has been shown in clinical exercise trials that high-impact training can efficiently increase bone mineral mass or density. However, relatively few studies have been published to report how high-impact training effects on bone strength, and is this type of exercise feasible in augmenting bone strength and cartilage quality in postmenopausal women. In this 12-month RCT, we examined whether progressive high-impact training (3x / week) could improve postmenopausal women's femoral neck structural strength and estimated biochemical composition of knee cartilage. Eighty postmenopausal women with mild knee radiographic osteoarthritis were randomly assigned to the exercise (n = 40) or the control group (n = 40). Femoral neck structural traits were assessed with DXA. Knee cartilage region exposed to exercise loading was measured by quantitative MRI techniques of T2 mapping and dGEMRIC. In addition, an accelerometer-based body movement monitor was used to evaluate the overall physical activity loading in all participants throughout the study period. Training effects on outcome variables were estimated by the bootstrap analysis of covariance (ANCOVA). Significant between group difference in favour of the trainees was observed after the 12-month intervention in femoral neck bending strength (4.4%, $p < 0.01$). The change in femoral neck bending strength remained significant after adjusting for baseline value, age, height and body mass (4.0%, $p = 0.020$). In all participants the change in bending strength associated with overall physical activity loading ($r = 0.29$, $p = 0.012$). The exercise intervention had no effect on estimated knee cartilage biochemical composition, as investigated by quantitative MRI. In conclusion, the high-impact training increased femoral neck strength without having any harmful effects on knee cartilage composition in women with mild knee osteoarthritis. These findings suggest that progressive high-impact exercise is feasible in the prevention of hip fractures in postmenopausal women who may also have frail articular cartilages.

KEYWORDS: RCT; EXERCISE; MENOPAUSE; BONE STRENGTH; CARTILAGE.

1 INTRODUCTION

Osteoarthritis (OA) is debilitating disease particularly in the weight-bearing joints of the knees. Knee pain and other symptoms often reduce mobility such as in walking.[1,2] Reduced mobility, in turn, changes the bone loading environment at the affected lower limb. It is well acknowledged, that decreased loading decrease bone mineral mass and more importantly, bone strength in loading related site specific fashion.[3-5] There is an increasing body of evidence, that in certain population OA and osteoporosis (OP) are not necessarily mutually exclusive.[6,7] For example, in large epidemiological study among postmenopausal women with fragility fractures, the presence of hip OA was seen on X–rays.[8] OA and OP coexist among postmenopausal women more than any other subject group, and it has been suggested that changes in estrogen level might be the common hormonal link in the development of these diseases.[9] Thus, femoral neck strength is of great clinical importance in terms of fracture prevention in postmenopausal women with knee OA, and who may be at risk of OP. After all, hip fractures represent the most serious consequence of bone loss, i.e., strength decrease, from individual's perspective[10,11] and causes also huge economic burden for society.[12]

Exercise is recommended among the key treatment strategies for preventing and treating OP in postmenopausal women.[13-15] To date, relatively few studies have been published to report how exercise effects on femoral strength in postmenopausal women. In those few existing RCTs with various participants characteristics of postmenopausal women,[16-18] the effect of exercise on femoral neck strength have been inconsistent, and firm conclusions cannot be made based on these findings. Likewise, in knee OA exercise is recommended as one of the most important management in the current treatment guidelines.[19] Although exercise is effective in short-term pain alleviation and improving physical function,[20,21] little is known on the effects of exercise on knee cartilage, a hallmark feature of early pathological changes in OA. Referring to subjects with mild OA, and who are at risk of OP, the question often raises, can bone and cartilage properties augmented or maintained simultaneously by the same exercise modality?

In a recent study, we showed that the progressive high-impact exercise lowered fall risk factors by increasing physical function, and increased femoral neck bone mineral mass in postmenopausal women with mild knee OA.[22] However, since bone mass is only one

determining factor of the bone strength, it is important to examine the exercise response to other bone strength traits as well. On the other hand, high-impact exercise program had no positive or negative responses on knee cartilage in detailed subregion analysis. Moreover, since there is no canonical standard procedure for defining cartilage regions-of-interest (ROIs) in knee OA, more comprehensive ROI definition approach is needed to be able to detect potential cartilage responses to mechanical loading. In the present study, the aim is to investigate the effects of the exercise on femoral neck bone structure, and biochemical properties of the whole cartilage region exposed to mechanical loading. Thus, we are asking whether a 12-month high-impact exercise program is effective in increasing femoral neck structure and in enhancing biochemical properties of the knee cartilage in postmenopausal women with mild knee OA.

2 METHODS & MATERIALS

This study was a comprehensive analyze of a 12-month randomized controlled trial with two experimental group; a high-impact exercise group and a control group (ISRCTN58314639). The targeted training frequency was three times per week for 12 months. The measurements were performed at baseline, and at the end of the 12-month intervention. Detailed study protocol has been described elsewhere,[22] but briefly, the participants were recruited from the Jyväskylä region in Central Finland through newspaper advertisements, and a total of 298 postmenopausal women indicated their interest in the study. A total of 80 volunteers met the inclusion criteria after assessing their eligibility by a telephone interview, a clinical examination screening, radiographs from the tibiofemoral joint and lumbar spine and femoral neck DXA-scanning. The criteria for eligibility were: postmenopausal woman, 50-65 years of age, knee pain on most days, leisure time physical activity no more than two weekly sessions of intensive exercise, no contraindications to exercise and no illnesses that would limit their participation in the exercise program, and Kellgren/Lawrence (K/L) 1-2 radiographic grading of the tibiofemoral joint OA.[23] The exclusion criteria were: osteoporosis, body mass index above 35 kg/m², knee surgery or instability, inflammatory joint disease, recent intra-articular steroid injections in the knee, contraindications to MRI or contrast agents. The trial profile is presented in Fig. 1.

Figure 1 comes here.

The study protocol was approved by the Ethics Committee of the Central Finland Health Care District (Dnro1E/2008). The protocol conformed to the principles of the Declaration of Helsinki. Written informed consent was obtained from all of the participants.

A priori statistical power calculations were based on DXA-measured femoral neck bone mineral content, and indicated that 35 participants in each group were required to detect a 0.08 gram (~2%) difference in change between the intervention and the control group (α=0.05, power=80%), considering a drop-out rate of approximately 10%. The participants were randomly assigned to the exercise group (N = 40) or the control group (N = 40) using

computerized block randomization. A block size of 10 stratified according to K/L grade 1 and 2 was used. Two participants from the exercise group withdrew immediately after randomization and two trainees dropped out during the study, while none dropped out from the control group (Fig. 1).

Exercise intervention

The exercise group participated in three weekly 55 min long sessions of supervised high-impact aerobic and step-aerobic exercise programs for 12 months[22] similar to what we have applied previously.[16,17,24] The practical training included high-impact loading (jumping exercises), as well as rapid change of movements with music. The loading was gradually increased over the course of the intervention in 3-month periods by increasing the stepping height, and the height of the obstacle that the participants were asked to jump over. Mean training compliance was 68% and the mean training frequency was 2.1 (SD 0.9) per week (with withdrew trainees included). The exercise program has been described in details elsewhere.[22]

Bone strength assessement

Femoral neck was scanned with dual-energy X-ray absorptiometry (DXA, GE Medical Systems, Lunar Prodigy, Madison, WI, USA) in both hips. Subsequently femoral neck cross sectional area (CSA, [mm^2], the surface area of bone in the cross-section after excluding all trabecular and soft tissue space), section modulus (Z, [mm^3]), an index of bending strength), and subperiosteal width (W, [mm], outer diameter of the bone after correcting for image blur) were calculated with Advanced Hip Analysis (AHA). The coefficient of variation for repeated measurements of various AHA variables has been reported to be less than 3%.[25]

Knee cartilage assessment

Transverse relaxation time (T2) and dGEMRIC index; ie., spin lattice relaxation time (T1) in the presence of gadolinium were determined using a Siemens Magnetom Symphony Quantum 1.5 T scanner (Siemens AG, Medical Solutions, Erlangen, Germany); a detailed description has been published elsewhere.[22] Briefly, T2 mapping was performed using a sagittal multislice multiecho fast spin echo sequence. Two slices, each covering the central region of

the medial or lateral femoral condyles, were analyzed. For dGEMRIC measurements, an intravenous administration of 0.4 ml/kg of Gd-DTPA^{2-} (Magnevist, Schering, Berlin) was followed by active knee motions for 15 min. After a 90-minute delay from injection T1 relaxation time measurements were performed by using a single slice inversion recovery fast-spin echo sequence from same topographical location as T2 slices. All scans were performed on the side with the higher K/L grade knee.

dGEMRIC and T2 maps were generated using an in-house MATLAB application (Mathworks, Inc. Natick, MA, USA). dGEMRIC index and T2 are given with results averaged across sagittal view of regions-of-interest (ROIs) in the medial and lateral femoral condyles. Both ROIs included full-thickness cartilage entity (hereafter called bulk cartilage) mainly exposed to mechanical loading according to the high-impact exercise program. ROI was drawn manually yielding from the outer edge of the anterior horn of the meniscus to the midpoint of the posterior femoral cartilage (the posterior femoral cartilage ranges from the outer edge of the posterior horn of meniscus up to the posterior top corner of the cartilage) (Fig. 2). The dGEMRIC indices were corrected by body mass index.[26] Generally, dGEMRIC index is reported to decrease with a lowered glycosaminoglycan (GAG) content of the cartilage.[27] Correspondingly, T2 is reported to elevate with a degeneration of the cartilage.[28,29] The inter-observer error (CV_{RMS}) in our laboratory for T2 full-thickness ROI was on average 2% and 3% for dGEMRIC.

Figure 2 comes here.

Physical activity assessment

Daily physical activities were recorded at four and ten months from intervention start for three consecutive days by recording the number and intensity of vertical acceleration peaks (impacts) using an accelerometer-based body movement monitors (Newtest, Oulu, Finland) in all participants (intervention training classes not included). During the three day measurements the participants wore the monitors attached to a waist belt while performing normal day-to-day activities. Monitor was taken off at bedtime or when it might get wet. The participants were also asked to keep a diary when the monitors were worn on and to list all activities included into measurements. The number of peaks was divided into 32 different

acceleration level bins (0 g to 9.3 g) and the number of impacts in each acceleration level bin was calculated. Daily impact score was calculated for the daily physical activity using the logarithmic relationship (DIS_{Log})[30] between loading numbers and magnitude equation as:

$$DIS_{Log} = \sum_{i=1}^{32}(a_i + 1)ln(N_i + 1),$$

where a_i = the higher cutoff of the i^{th} acceleration level bin and N_i = number of acceleration peaks within the i^{th} acceleration level bin. One was added to the acceleration measured with the accelerometer-based body movement monitor in the DIS_{Log} calculations, since the accelerometer gives 0 g while standing still, whereas the muscles still have to counteract the 1 g caused by gravitation. There was no difference between the groups in average daily physical activity throughout the 12-month study period outside the intervention training classes given as DIS_{Log}.[22]

The aerobic and step-aerobic exercise loading was quantified by recording the number and intensity of acceleration peaks (impacts) with accelerometer-based body movement monitors (Newtest, Oulu, Finland) during one exercise session in every 3-month period. The number of impacts were combined to five acceleration levels according to Vainionpää et al.[40] to describe the different patterns of physical activity; 0.3-1.0 g (e.g., walking), 1.1-2.4 g (e.g., stepping), 2.5-3.8 g (e.g., jogging), 3.9-5.3 g (e.g., running, jumping), and 5.4-9.3 g (e.g., jumping, drop-jumping). In addition, total physical activity loading index DIS_{Total} was calculated to describe participants' all physical activity over the study period (i.e., exercise program and physical activity) using the same formula which was used to calculate the daily physical activity. For the control participants the DIS_{Total} = DIS_{Log}, since they were not involved in the exercise intervention.

Questionnaires

Health-related quality of life (HRQoL) was assessed using the Finnish version of the validated RAND 36 item health survey 1.0 questionnaire (RAND-36).[31] RAND-36 is a generic questionnaire comprising 8 distinct dimension of health status: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role limitations (emotional), mental health, and role limitations (physical). The scale is from 0 to 100, so that a high score on a scale represents higher HRQoL. Clinically important symptoms of knee

pain, stiffness and physical function were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[32] We reported earlier that after the 12-month trial, there were no intergroup differences in knee pain, stiffness, or physical function.[22]

Statistical analysis

Data were examined using SPSS 20.0.0.2 (IBM Corp., Armonk, NY). All analyses were based on intention-to-treat principles. Means and standard deviations are given as descriptive statistics. Epps-Singleton two-sample test was used to examine the equality of distributions for total physical activity loading index (DIS_{Total}) in the exercise group and the control group. Statistical comparison of changes in bone strength indices and quantitative MRI were performed by using the bootstrap analysis of covariance (ANCOVA); because of the violation of distributions assumptions. Thus the confidence intervals (95% CI) for bone and MRI outcome means were obtained by bias corrected bootstrapping (5000 replications). Baseline value of the variable of the interest and baseline height, body mass and age were used as covariates in ANCOVA. The association between DIS_{Total} and the changes in bone and cartilage indices were examined with Pearson correlation coefficient. The level of statistical significance was set at $\alpha \leq 0.05$.

3 RESULTS

Baseline characteristics for the study groups are given in Table 1. No differences were found between the exercise group and the control group in the descriptive or clinical characteristics at baseline.

Table 1 comes here.

In the exercise group the mean number of exercise program acceleration peaks over the 12-month exercise intervention period was 1713 (SD 337) at 0.3-1.0 g acceleration level, 401 (33) at 1.1-2.4 g acceleration level, 76 (5) at 2.5-3.8 g acceleration level, 41 (7) at 3.9-5.3 g acceleration level, and 44 (16) at 5.4-9.3 g acceleration level. The exercise program and physical activity loading, i.e., DIS_{Total}, was significantly higher (364 [73]) in the exercise group than that in the control group (168 [46], $P < 0.01$), indicating that the group difference in impacts is due to the exercise program. The percentage distribution of average DIS_{Total} for the exercise group and the control group is shown in Fig. 3.

Figure 3 comes here.

The baseline values and the treatment effect of bone strength indices are given in Table 2. The adjusted treatment effect (mean [95% CI]) in femoral neck Z was 23 (4 to 42) mm^3 in favor of the exercise group, while no significant differences were observed between the groups in femoral neck CSA or W after the intervention (Table 2). The total physical activity loading (DIS_{Total}) was positively associated with the change of the Z ($r = 0.29$, $p = 0.012$), whilst no significant associations were observed between DIS_{Total} and changes of femoral neck CSA or W.

Table 2 comes here.

The baseline values and the treatment effects of cartilage indices are given in Table 2. After 12 months there were no significant differences between the groups in bulk cartilage values in the medial or lateral condyle either with T2 or dGEMRIC mapping variables (Table 2). There were no statistically significant relationships between total physical activity loading (DIS_{Total}) and changes in T2 in the medial condyle ($r = 0.12$, $p = 0.30$) or lateral condyle ($r = 0.05$, $p = 0.65$), or in dGEMRIC index in the medial ($r = 0.15$, $p = 0.20$) or lateral condyle ($r = 0.20$, $p = 0.09$).

In cartilage and bone relationship, there was an association between change in T2 value at medial femoral condyle and Z, showing that Z increased with decreasing T2 relaxation time ($r = -0.32$, 95% CI: -0.55 to -0.04) (Fig. 4). In addition, there was an association between change in dGEMRIC index at lateral femoral condyle and Z, showing that Z increased with increasing dGEMRIC index ($r = 0.24$, 95% CI: 0.02 to 0.46) (Fig. 4).

Figure 4 comes here.

4 DISCUSSION

The primary finding of the present study was that femoral neck strength can be positively modified with a high-impact exercise in postmenopausal women with mild knee OA. In addition, the applied high-impact training turned out to be safe for the bulk cartilage area exposed to loading, which is in line with our recent results[22] with the very same group and intervention, that high-impact loading was not harmful for load-bearing cartilage subregions. It is also noteworthy, that the overall physical activity during the study was related to femoral neck strength improvement in all participants.

To date, there are a limited number of randomized controlled exercise intervention trials with postmenopausal women, where the effects of exercise or physical activity on femoral strength have been evaluated. In previous RCTs in early postmenopausal women[16], older postmenopausal women[17] and breast cancer pre- and postmenopausal women[18] femoral neck exercise induced strength improvements have not consistently demonstrated, in contrast to our study showing a significant exercise effect on femoral neck strength. To some extent these inconsistent results may be explained by different group characteristics, exercise compliance or training intensities. In the present study, we were able to quantify the actual exercise loading of the trainees throughout the trial by using the accelerometer-based body movement monitors. On the contrary, our finding is in line with our previous study in premenopausal women, where we observed a 3% increase in femoral neck section modulus following an 18-month high-impact exercise intervention[33] similar to the one utilized in the present study. Further, since improvement in pQCT derived bone mass and geometry have been consistently found following weight-bearing jumping exercises in premenopausal women[34] and postmenopausal women,[35] it is plausible that the high-impact loading regime in the present study is the primary reason for observing the positive response in femoral neck bending strength.

In addition to the exercise induced positive response on femoral neck bending strength, the training was able to maintain, although not statistically significantly, femoral neck CSA reflecting sustainable strength abilities against compressive force. In contrast, exercise had no effect on outer diameter (W) of femoral neck. These findings may indicate that increased loading over the 12-month training period has led to reshaping of the bone cross-section and a redistribution of bone minerals from trabecular to cortical component without any external

expansion. Unfortunately we had no opportunity to verify this assumption by QCT-measurement, which is capable to analyze cortical and trabecular bone separately. However, our result of the load-bearing femoral neck in response to mechanical loading exposure is in line with our previous results in sedentary premenopausal women,[33] premenopausal female athletes representing high-impact and odd-impact loading sports,[36] and national-level female and male triple jumpers.[37] The common feature for the femoral neck strengthening studies is that the skeleton has been exposed to activities involving jumps and versatile movements with relative high ground-reaction forces from 2 to 6 times body weight in pre- and postmenopausal women,[22,24] and up to 14 to 22 times body weight in triple jumpers.[37] These findings confirm the earlier observations, that in order to achieve an osteogenic bone response, the loading-induced mechanical deformation i.e., strains needs to be of a high magnitude and a high/fast rate.[38,39]

The quantifying of study participants' coverall physical activity (i.e. frequency, intensity and duration) over an intervention trial is often a challenging task due to somewhat indirect physical activity meters. In the present study we used a previously validated method for describing the individual daily osteogenic loading with a single score DIS_{Log}.[30] We found an association between the femoral neck bending strength change and the total physical activity loading index DIS_{Total}. In other words, the more in amount, and the higher in intensity the subjects' daily physical activity included impacts, the bigger became their femoral neck bending strength. The present finding is in line with the finding by Ahola et al.,[30] who reported an association between the individually specific loading measured by accelerometer-based body movement monitor i.e., DIS_{Log} during a high-impact exercise intervention and the osteogenic response at the throcanter.[30] Unfortunately, there is a relative paucity of the literature on the topic at the moment, but previous exercise study by Vainionpää et al.[40] measuring physical activity at different acceleration levels revealed that in healthy premenopausal women physical activity including accelerations exceeding 3.9 g forces induced positive response in femoral neck BMD. Less than 100 accelerations per day were needed to improve hip BMD over threshold level at 3.9 g.[40] The findings from the aforementioned studies indicate that monitoring the performance technique and consequent loading during the exercise regime either as DIS_{Log} or absolute values may be useful indicator of the osteogenic potential to be expected.

Further analyzes on cartilage responses to exercise were also carried out in this study in relation to our previously published cartilage results.[22] Our previous results had been gained from the load-bearing cartilage regions which had been divided into several subregions based on certain anatomical landmarks, whilst in the current study rather same region in the medial and lateral femoral condyles were analyzed as unite topographical entities. The current cartilage ROI division was based on functional adaptation premise, in which femur provides the bearing surface of several reaction forces in knee joint. During standing and walking, the central part of the femoral cartilage is in contact with the tibia cartilage or meniscus, and during knee flexion the reaction forces are transmitted more posteriorly to the femoral cartilage.[41] Because our exercise protocol included a lot of both vertical loading and knee bending ranging from nearly full extended 5° to 70° flexion, we studied the femoral cartilage areas which were most highly exposed areas to exercise loading, and therefore most clinically relevant zones with regard to OA. We have also previously shown that bigger cartilage ROIs have higher measurement accuracy than smaller ROIs,[42] being therefore more subtle to detect possible cartilage responses. Nonetheless, as a result the bulk cartilage regions remained unchanged as was seen in our earlier analyses with several cartilage subregions. However, in the correlation analysis of the present study, we found that with an increase of the femoral neck strength, the surrogate for knee cartilage constituent (T2) decreased in medial femoral condyle corresponding to favorable cartilage collagen integrity and water content.[43,44] Similarly, there was an association between femoral neck strengthening and elongating of cartilage dGEMRIC index in lateral femoral condyle corresponding to increase in GAG content. Although the exercise program per se had no effects on bulk cartilage areas and the aforementioned bone-cartilage associations remained rather fair level, these findings imply with this population of women having mild knee OA that osteogenic exercise and physical activity in general, is likely to have more favorable than detrimental effects on knee cartilage biochemical composition. Due to paucity of RCTs investigating exercise effects on knee cartilage in OA, further studies are needed to investigate the optimal type and dose of exercise for cartilage health.

This study has several strengths as we have pointed out previously,[22] that is, this is the first RCT in OA subjects investigating the effects of exercise directly at knee cartilage level, the study design fulfills all the important quality criteria of RCT, the intervention is sufficient of duration and with high training compliance, and there were only a few dropouts. The limitation of the study is that using DXA-based AHA analysis to evaluate femoral neck bone

structure, it is impossible to distinguish effects of high-impact loading on redistribution of bone minerals between trabecular component and cortical component. In addition, bone trait change in the complex three-dimensional hip is not likely to be accurately depicted on the basis of data extracted from two-dimensional DXA scan. These inaccuracies related to imaging techniques, however, can be at some extent overcome in this study with appropriately powered study design. Limitations related accelerometer-based measurements were that only one aerobic and step-aerobic training session was recorded per trainee per quarter for the exercise impact score determination in order to describe the overall loading level of the exercise regimen. In addition, in daily physical activity measurements three consecutive days of accelerometer-based recording may not be representative of habitual levels of physical activity. Moreover, rather coarse total physical activity index was comprised in describing all activities throughout the study by including into the same index the average loadings from the exercise intervention and daily physical activities. Furthermore, since accelerometer measures gravitational forces only, part of daily physical activities may not have captured due to meter's inability to gauge static work or activities which do not contain much acceleration forces such as in climbing, cycling or skiing. However, by the information from physical activity diaries we were able to ascertain that there were no differences in daily physical activities between the groups, and that the monitors did not become falsely activated for example while riding or driving motor vehicles. Finally, it should be kept in mind that even the body movement monitor does not provide more than a description of different human activities, it is advantageous in quantifying individual ambulation with an osteogenic loading.

In conclusion, high-impact exercise can modulate femoral neck strength in a positive manner in postmenopausal women. In addition, hip strengthening was associated to overall total physical activity over one year study period; the more there was impact containing physical activity assessed using an accelerometer-based body movement monitor, the higher became femoral neck strength. The progressive high-impact training proved to be safe for cartilage health in mild knee OA, since the exercise did not alter in any way the biochemical composition of the cartilage region exposed to loading. These findings in conjunction with our previous results that training improved physical function suggests that high-impact exercise may be feasible in prevention of hip fractures by increasing femoral neck bone strength, and by reducing physical performance related risk factors for falls in postmenopausal women with mild knee OA.

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Authors' roles: AHeinonen, AHäkkinen, IK, MTN, TJ and JM designed the research; JM, AHeinonen, MTN, EL and TJ conducted the research; JM, TR and RA collected the data; HK, AHeinonen, JM and TR analyzed the data and performed statistical analysis; JM, AHeinonen, TR MTN, HK, AHäkkinen and IK interpreted the data; JM and TR drafted the manuscript; JM, TR, AHeinonen and AHäkkinen revised the manuscript content; all authors approved the final version of the manuscript; JM and AHeinonen take responsibility for the integrity of the data analysis.

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FIGURES AND TABLES

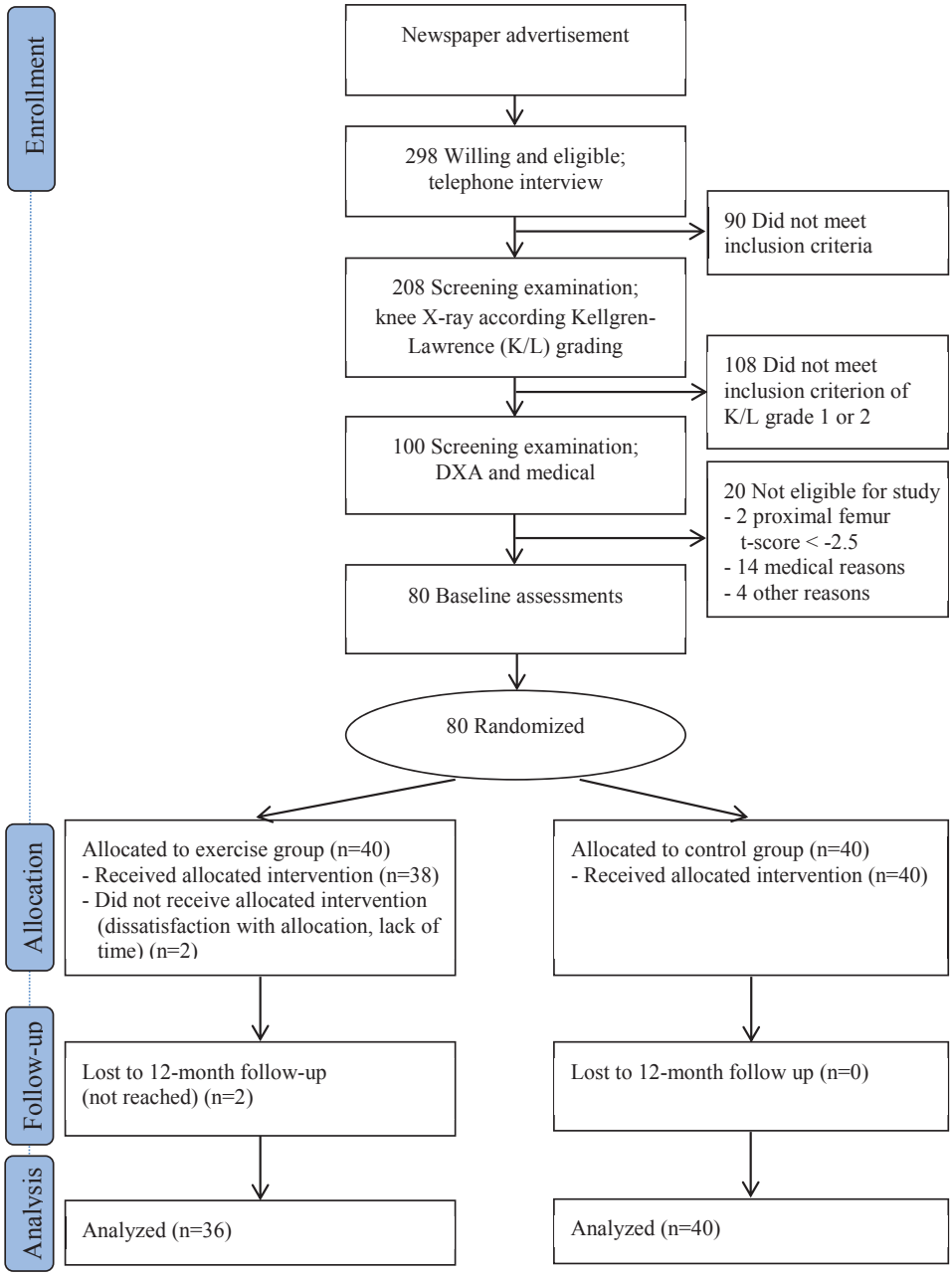

Figure 1. Trial profile.

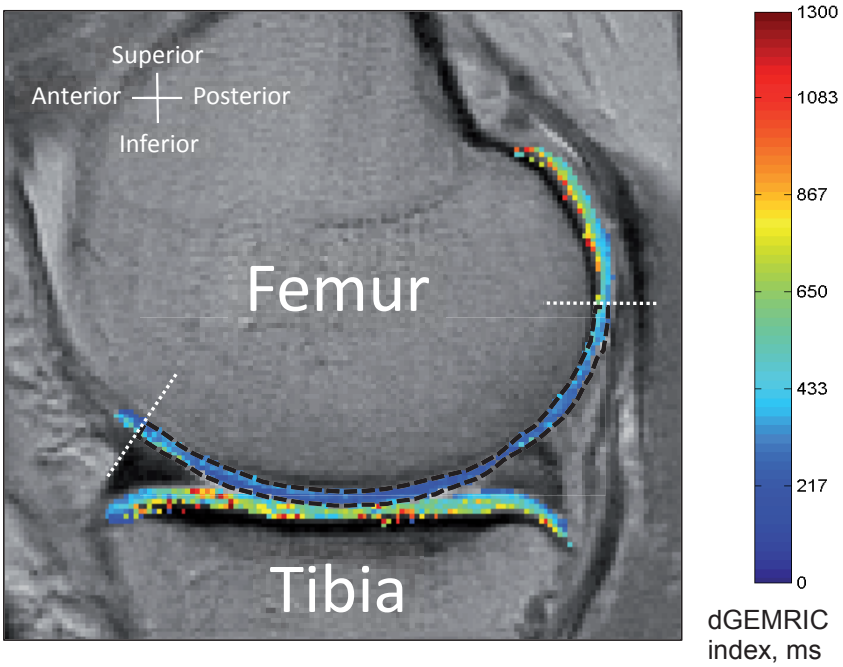

Figure 2. Cartilage region-of-interest (ROI) in a single sagittal slice from the center of the medial femoral condyle. The ROI is confined across full-thickness cartilage from the outer edge of the anterior horn of the meniscus to the midpoint of the posterior femoral cartilage, as outlined by the dashed lines. In delayed gadolinium enhanced MRI of cartilage (dGEMRIC) high values correspond to high glycosaminoglycan (GAG) content and low values correspond reduced GAG content.

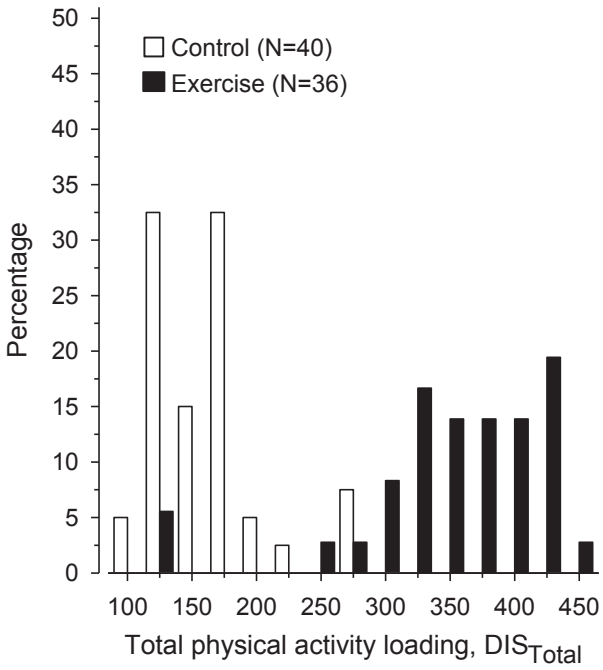

Figure 3. Percentage distribution of the total physical activity loading index (DIS_{Total}) for the control group and the exercise group over the 12-month study period. In the controls, DIS_{Total} is the same as the average daily impact score (DIS_{Log}) while in the exercisers it includes DIS_{Log} and the average impact loading of the exercise intervention.

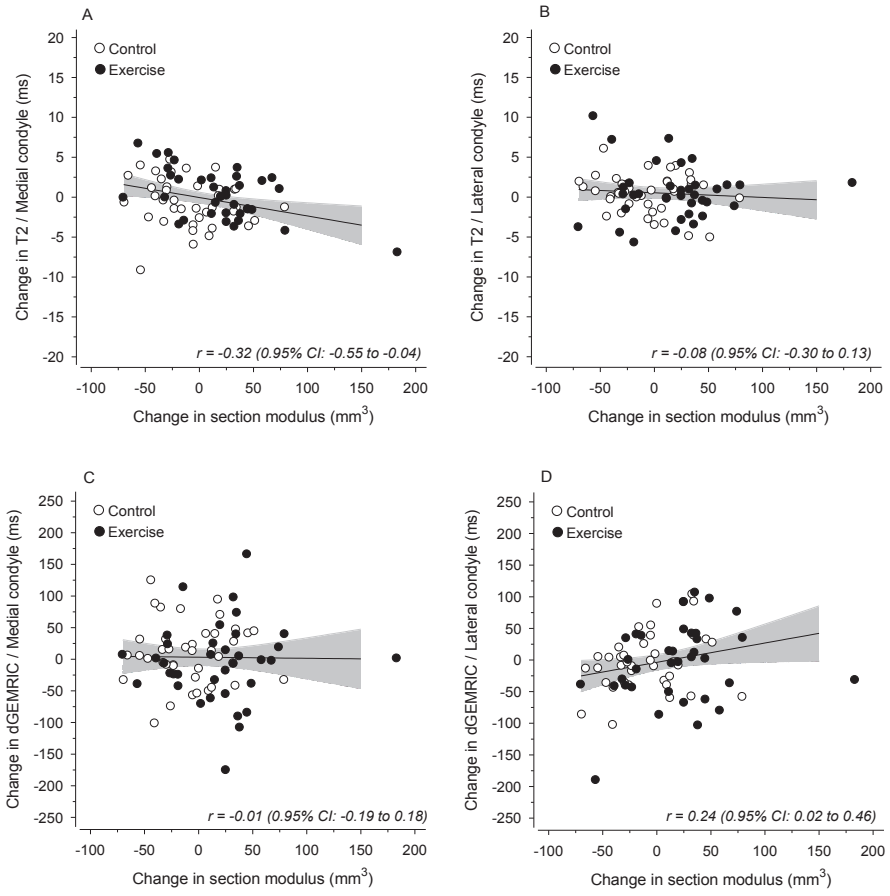

Figure 4. Associations between change in the femoral neck section modulus and change in T2 (upper row) and dGEMRIC indices (lower row) for bulk femoral cartilage.

Table 1. Descriptive and clinical characteristics (mean, SD) at baseline in the exercise and the control groups.

Characteristics	Exercise N = 38	Control N = 40
Age [years]	57.9 (4.2)	58.8 (4.2)
Body mass [kg]	73.4 (9.4)	69.4 (11.7)
Height [cm]	165 (6)	161 (5)
Body mass index [kg/m^2]	27.1 (3.1)	26.7 (4.2)
Kellgren Lawrence grade, n [%]		
Grade 1	12 (32)	13 (32)
Grade 2	26 (68)	27 (68)
RAND-36[a] Item		
General health	74.1 (11.0)	73.6 (14.0)
Physical functioning	89.9 (9.1)	90.6 (10.3)
Emotional well-being	83.9 (11.2)	83.3 (12.9)
Social functioning	88.9 (17.9)	94.7 (11.3)
Energy	70.4 (16.2)	75.4 (14.2)
Pain	80.5 (12.7)	83.1 (14.7)
Role physical	88.5 (21.7)	91.3 (22.3)
Role emotional	84.7 (27.9)	89.2 (30.6)

[a]RAND 36 item health survey questionnaire

Table 2. Baseline, follow-up, and treatment values of DXA-derived femoral neck hip structural analysis (HSA) and dGEMRIC Index and T2 from the medial and lateral weight-bearing bulk femoral cartilages.

	Baseline, Mean (SD)		Follow-up Mean (SD)		Treatment effect		p-value	
Variable	Exercise (n=36)	Control (n=40)	Exercise (n=36)	Control (n=40)	Crude mean (95% CI)	Adjusted[a] mean (95% CI)	Crude	Adjusted[a]
DXA HSA								
Z [mm^3]	640 (146)	609 (109)	658 (148)	600 (110)	28 (11 to 47)	23 (5 to 41)	0.003	0.020
CSA [mm^2]	153 (24)	143 (20)	153 (23)	141 (19)	2 (-0 to 5)	3 (-0 to 5)	0.079	0.096
W [mm]	49.2 (4.2)	48.9 (4.8)	48.7 (4.1)	48.8 (4.7)	-0.3 (-1.2 to 0.6)	-0.4 (-1.4 to 0.7)	0.48	0.49
quantitative MRI								
dGEMRIC [ms]								
Medial	453 (54)	469 (53)	457 (67)	459 (64)	10 (-15 to 36)	10 (-15 to 36)[b]	0.47	0.45[b]
Lateral	458 (57)	466 (46)	460 (44)	468 (52)	-5 (-24 to 15)	-8 (-26 to 12)[b]	0.61	0.44[b]
T2 [ms]								
Medial	51.2 (3.7)	50.0 (4.6)	51.5 (5.2)	49.4 (3.9)	1.1 (-0.3 to 2.5)	1.3 (-0.1 to 2.7)	0.12	0.088
Lateral	49.4 (4.2)	49.9 (3.5)	50.0 (5.1)	50.4 (3.6)	-0.4 (-2.5 to 1.6)	-0.6 (-2.6 to 1.3)	0.69	0.54

[a]Adjusted by baseline value, age, height and body mass, [b]Adjusted by baseline value and age only.