

JYU DISSERTATIONS 35

Matti Munukka

Exercise as Stimulus for Cartilage Health in Knee Osteoarthritis



UNIVERSITY OF JYVÄSKYLÄ
FACULTY OF SPORT AND
HEALTH SCIENCES

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Editors

Ina Tarkka

Faculty of Sport and Health Sciences, University of Jyväskylä

Ville Korkiakangas

Open Science Centre, University of Jyväskylä

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ABSTRACT

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Finnish summary

Diss.

Knee osteoarthritis (OA) is a leading cause of musculoskeletal pain and disability and has significant socio-economical costs globally. There is no known cure for OA. Therapeutic exercise has been shown to evoke acute positive post-treatment effects on pain and function. Even though cartilage degeneration is crucial in OA progression, there is sparse knowledge about exercise effects on osteoarthritic cartilage. The purpose of this study was to investigate the efficacy of aquatic resistance training on the estimated biochemical composition of tibiofemoral cartilage and the association between leisure time physical activity (LTPA) and tibiofemoral cartilage in postmenopausal women with mild knee OA.

This study utilizes data from a large randomized controlled trial (RCT) intervention project, AquaRehab (ISRCTN65346593). In 4-month progressive aquatic resistance training (RCT) and in 12-month LTPA follow-up studies, the biochemical composition of the knee cartilage was evaluated using T2 relaxation time and dGEMRIC index quantitative MRI methods in 87 postmenopausal women with mild knee OA. Cardiovascular fitness, muscle force, symptoms, quality of life and self-assessed function were also measured. Additional data from our previous RCT intervention project, LuRu (ISRCTN58314639), was utilized in a cross-sectional study assessing the association between neuromuscular performance and lower limb bone strength in 139 postmenopausal women with mild knee OA.

The 4-month progressive aquatic resistance training resulted in positive regional changes in mildly osteoarthritic knee cartilage and improved cardiorespiratory fitness. Also, there was a significant decrease in self-assessed stiffness in the training group compared to controls. In addition, higher LTPA level was related to regional improvements in knee cartilage quality during a 12-month follow-up period. Further, neuromuscular performance predicted lower limb bone strength in every measured skeletal site in women with knee OA.

In conclusion, continuously implemented physical activities may result in regional adaptation in mildly osteoarthritic knee cartilage and a positive effect on cardiorespiratory fitness and self-assessed knee stiffness.

Keywords: osteoarthritis, cartilage, physical activity, postmenopausal women

Author's address

Matti Munukka, MSc, pt
Faculty of Sport and Health Sciences
University of Jyväskylä
P.O Box 35
FI-40014 University of Jyväskylä, Finland
matti.munukka@jyu.fi

Supervisors

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

Professor Arja Häkkinen, PhD
Faculty of Sport and Health Sciences
University of Jyväskylä, and
Department of Physical Medicine and Rehabilitation
Central Finland Health Care District
Jyväskylä, Finland

Reviewers

Professor Rana Hinman, PhD
Department of Physiotherapy
University of Melbourne
Melbourne, Australia

Professor Carl Johan Tiderius, PhD
Department of Orthopaedics
Lund University
Lund, Sweden

Opponent

Professor Jari Arokoski, MD, PhD
Department of Physical and Rehabilitation Medicine
Helsinki University Hospital and University of Helsinki
Helsinki, Finland

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Jyväskylä, August 2018

Matti

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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 Munukka M*, Waller B*, Rantalainen T, Häkkinen A, Nieminen M.T, Lammentausta E, Kujala U.M, Paloneva J, Sipilä S, Peuna A, Kautiainen H, Selänne H, Kiviranta I & Heinonen A. Efficacy of a Progressive Aquatic Resistance Training for Tibiofemoral Cartilage in Postmenopausal Women with Mild Knee Osteoarthritis: A Randomised Controlled Trial. *Osteoarthritis and Cartilage* 2016; 24(10):1708-17.
- II Munukka M, Waller B, Häkkinen A, Nieminen M.T, Lammentausta E, Kujala U.M, Paloneva J, Kautiainen H, Kiviranta I & Heinonen A. Effects of Progressive Aquatic Resistance Training on self-assessed function and quality of life in postmenopausal women with mild knee osteoarthritis - A Randomised Controlled Trial with 12-month follow-up. Submitted for publication 2018.
- III Munukka M, Waller B, Häkkinen A, Nieminen M.T, Lammentausta E, Kujala U.M, Paloneva J, Kautiainen H, Kiviranta I & Heinonen A. Physical Activity Is Related with Cartilage Quality in Women with Knee Osteoarthritis. *Medicine & science in sport & exercise* 2017; 49(7):1323-30.
- IV Munukka M, Waller B, Multanen J, Rantalainen T, Häkkinen A, Nieminen M.T, Lammentausta E, Kujala U.M, Paloneva J, Kautiainen H, Kiviranta I & Heinonen A. Relationship between lower limb neuromuscular performance and bone strength in postmenopausal women with mild knee osteoarthritis. *Journal of Musculoskeletal and Neuronal Interactions* 2014;14(4):418-24.

* Equal contribution.

ABBREVIATIONS

ADL	Activities of daily living
AHA	Advanced hip analysis
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AquaRehab	Research project investigating the effect of aquatic exercise in postmenopausal women with mild knee osteoarthritis
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Bone mass index
BSI _d	Distal tibia compressive bone strength index
BW	Body weight
CI	Confidence interval
cm	Centimeter
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
DXA	Dual-energy x-ray absorptiometry
ECM	Extracellular matrix
ES	Effect size
ETL	Echo train length
FOV	Field of view
GAG	Glycosaminoglycan
Gd-DTPA ²⁻	Gadolinium embedded diethylene triaminopentaacetate acid
GRF	Ground reaction force
ICC	Intra-class correlation coefficient
kg	Kilogram
K/L	Kellgren and Lawrence
KOOS	Knee injury and osteoarthritis outcome score questionnaire
LTPA	Leisure time physical activity
LuRu	Research project investigating the effect of high-impact training in postmenopausal women with mild knee osteoarthritis
MAD	Mean amplitude deviation
METH	Metabolic equivalent task hour
MRI	Magnetic resonance imaging

min	Minute
mm	Millimeter
m	Meter
ms	Millisecond
N	Newton
OA	Osteoarthritis
OP	Osteoporosis
PA	Physical activity
PG	Proteoglycan
QOL	Quality of life
pQCT	Peripheral quantitative computed tomography
qMRI	Quantitative magnetic resonance imaging
ROI	Region of interest
ROM	Range of motion
RCT	Randomized controlled trial
RPE	Rate of perceived exertion
s	Second
SF36	The Short-form Health Survey
SD	Standard deviation
SMD	Standardized mean difference
SSI _{max} _{mid}	Tibial mid-shaft density weighted maximal moment of inertia
TAE	Therapeutic aquatic exercise
T	Tesla
TE	Echo time
TI	Inversion time
TR	Repetition time
T1	Spin-lattice relaxation time
T2	Transverse relaxation time
VO ₂ peak	Peak oxygen uptake
VAS	Visual analogue scale
WOMAC	Western Ontario and McMaster University Osteoarthritis Index
X-ray	Radiography
Z	Section modulus

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ORIGINAL PUBLICATIONS

1 INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis and a leading cause of pain and disability in older adults that develops slowly over years (Loeser et al. 2012). Knee OA accounts for 83% of the total OA burden and overall OA has significant socio-economical costs globally (Vos, Flaxman & Naghavi 2012, Litwic et al. 2013). OA is referred to as a slowly progressive degenerative joint disease (Loeser et al. 2012) and characterized by degeneration of articular cartilage, intra-articular inflammation with synovitis and changes in subchondral bone (Goldring & Goldring 2007). Also, biochemical changes in the composition of cartilage, such as decrease in the glycosaminoglycan content (GAG) and loss of integrity of collagen matrix, are characterized by early OA (Goldring & Goldring 2010). Further, it has been suggested that subchondral bone may have an important role in the progression of OA, as a mechanical damper and as a source of inflammatory mediators implicated in the OA pain process and in the degradation of the deep layer of cartilage (Berenbaum 2012).

OA is considered a whole-organ disease which is amenable to prevention, reducing the symptoms in early stages (Roos & Arden 2016). The prevalence of symptomatic knee OA and knee pain has approximately doubled in women and tripled in men over a period of 20 years (Nguyen et al. 2011). The prevalence of knee OA rises with age. The global prevalence of radiographically confirmed symptomatic knee OA was estimated to be 4.8% in females in 2010, and it peaked at around 50 years of age (Cross et al. 2014). In Finnish women, the prevalence of clinically diagnosed knee OA is 36% in the age group of 85 years and older (Arokoski et al. 2007). However, defining OA has proven to be problematic as in most research OA has been defined by radiographs without considering other structural findings (Roos & Arden 2016). Further, up to 50% of patients with radiographic knee OA do not experience regular pain and up to 50% with knee pain do not have any radiographic features of OA (Lawrence, Bremner & Bier 1966). Nevertheless, as the population ages throughout the world, larger numbers of osteoarthritic people require health services. Thus, preventive strategies, i.e. interventions, to control this socio-economic burden are needed.

There is no known treatment or cure for OA (McAlindon et al. 2014). Evidence-based clinical guidelines recommend weight loss, exercise and education as the early treatment of OA (Roos & Arden 2016), i.e., the focus of OA management is on the reduction of the symptoms and the decreased function associated with the disease (McAlindon et al. 2014). Irrespective of type (aerobic or strength) or modality (aquatic or land), therapeutic exercise has been shown to evoke acute posttreatment effects in achieving these goals (Uthman et al. 2013, Fransen et al. 2015). The biochemical properties of cartilage can be maintained with an active lifestyle with participation in exercise by both healthy humans (Tiderius et al. 2004, Teichtahl et al. 2009) and animals (Kiviranta et al. 1988, Brismar et al. 2003). Further, in a recent systematic review (Bricca et al. 2017) investigating the impact of a daily exercise dose on cartilage composition and thickness in healthy animals, it was shown that a high daily dose of exercise may have negative effects and a moderate daily dose positive effects on animal cartilage matrix composition. Even though the author highlighted that only 50% of findings from animal studies predict human outcomes, this promotes the need for further studies of humans in order to better understand the effects of different types and doses of exercise on articular cartilage. Randomized controlled trials on human cartilage are sparse (Roos & Dahlberg 2005, Multanen et al. 2014, Koli et al. 2015, Hawezi et al. 2016), but there are promising results showing that exercise interventions can improve the estimated biochemical properties of both tibiofemoral (Roos & Dahlberg 2005) and patellofemoral (Koli et al. 2015) cartilage. Importantly, despite the training modality and cartilage region investigated, none of the aforementioned exercise interventions were harmful to the knee articular cartilage and exercise was well tolerated by these study populations (Roos & Dahlberg 2005, Multanen et al. 2014, Koli et al. 2015).

The main purpose of this thesis was to investigate the efficacy of progressive 4-month aquatic resistance training on the estimated biochemical composition of tibiofemoral cartilage, physical function, OA-related symptoms and quality of life. Also, the association between 12-month leisure time physical activity (LTPA) and cartilage health in postmenopausal women with mild knee OA was investigated. As far as we know, no randomized controlled trial has been performed in OA population to investigate the efficacy of aquatic resistance training on the biochemical composition of tibiofemoral cartilage. Further, to our knowledge, we are also the first to follow participants' LTPAs daily during the 4-month intervention period and the 12-month follow-up period in this population. Better understanding of the interactions between physical activity and cartilage health in osteoarthritic population will produce practical help when assessing physical activity levels for cartilage-quality-related exercise interventions and also in clinical rehabilitation. Additional purpose of this thesis was to research whether neuromuscular performance predicted lower limb bone strength in different lower limb sites in postmenopausal women with mild knee OA.

2 REVIEW OF THE LITERATURE

The joints and the skeletal system represent important homeostasis by holding bones together in a way that allows for movement and flexibility (Tortora Derrickson 2006, 258-261). Joints are functional units that transfer mechanical loads and impacts, i.e. absorbs shocks, between adjacent bones during normal daily activities (Arokoski et al. 2000, Neumann 2002, Griffin & Guilak 2005). Bones provide rigid support for the human body, and due to their structure bones are able to bear huge amounts of weight (Tortora Derrickson 2006, 172). Joints are structurally classified as one of the following types (based on the presence or absence of a synovial cavity and the type of connective tissue that binds the bones together): 1. fibrous joints (immovable, no synovial cavity), 2. cartilaginous joints (allow little or no movement, no synovial cavity) and 3. synovial joints (highly mobile, synovial cavity) (Tortora & Derrickson 2006, 258-261). The majority of limb joints are synovial, such as the knee joint, and the articular surfaces of the bones are covered with articular cartilage (Palastanga, Field & Soames 2006, 23). In this doctoral thesis, which investigates relation between physical activity and knee OA, synovial knee joint is under close investigation.

2.1 Knee osteoarthritis

2.1.1 Anatomy and function of a knee joint

The knee joint, i.e. tibiofemoral joint, is the most complex and largest joint of the human body. It is a hinge joint which consists of three joints within a single synovial cavity: medial and lateral tibiofemoral joints and patellofemoral joint. In a knee joint, convex condyles on the distal end of the femur connect with two rounded concave condyles at the proximal end of tibia, permitting mainly flexion and extension movements with slight medial and lateral rotation. The patella lies proximal to the knee joint line when standing in a relaxed position, and

patellar ligament attaches between the apex of the patella and the tibial tuberosity. Femoral condyles articulate with the nearly flat surfaces of the tibia, which are held in place by an extensive ligamentous capsule and large muscles. Thus, the stability of the knee is based primarily on its soft tissue constraints rather than on its bony configuration. As foot is in direct contact with the ground, the soft tissues of the knee are often subjected to large forces from both external sources and muscles. Therefore, cartilage and ligament injuries are two common consequences of the large functional demands placed on the knee (Tortora & Derrickson 282-283, Neumann 434-436).

2.1.2 Articular cartilage

Articular cartilage is supplementary to bone, forming wherever rigidity, elasticity and strength are required. It is aneural and avascular tissue, which is nourished by tissue fluids (Tortora & Derrickson, 126-130). There are three main types of cartilage in the human body: hyaline, fibrous and elastic cartilage (Hall 2005, 33). In this doctoral thesis, "cartilage" or "articular cartilage" indicates hyaline cartilage as it is the most common cartilage and is typically found in a diarthrodial synovial joint. The role of knee cartilage is to bear burden, resist tensile, shear and compressive forces, distribute impacts to subchondral bone and allow bones to move smoothly against each other due to its nearly frictionless surface (Buckwalter, Mankin & Grodzinsky 2005, Eckstein, Hudelmaier & Putz 2006). Healthy cartilage is light, smooth, firm, slippery and elastic in order to ensure that bones move easily without friction (Loeser et al. 2012), and it is 2 to 4 mm thick depending on location (Fox, Bedi & Rodeo 2009).

Articular cartilage is connective tissue comprising of only one unique cell type, chondrocytes, which are embedded within a dense extracellular matrix (ECM) (Houard, Goldring & Berenbaum 2013). Chondrocytes make up about 1% of the volume of adult human cartilage and contain the organelles necessary for matrix synthesis. They are highly specialized metabolically active cells that play a unique role in the development, maintenance and repair of the ECM, even though cartilages ability to heal from injury or disease is generally poor. Chondrocytes also synthesize type II collagen, large aggregating proteoglycans (PG) (Buckwalter, Mankin & Grodzinsky 2005, Fox, Bedi & Rodeo 2009). ECM consists of two main components: tissue fluid, out of which 70-80% is water interacting with macromolecules and structural macromolecules such as type II collagen and the large aggregating PG aggrecans. The network of collagen fibers, mainly type II collagen, gives cartilage its tensile strength, stiffness and cartilaginous framework, whereas proteoglycans, with their highly negatively charged glycosaminoglycans (GAGs), provide compressive strength, viscoelasticity and lubricative traits allowing water to fill this molecular network as it can bind up to 50 times its weight in water (Buckwalter, Mankin & Grodzinsky 2005, Fox, Bedi & Rodeo 2009, Dahlberg et al. 2012).

Articular cartilage contains different zones with respect to depth from the articular surface and has a regional organization around the chondrocytes

(Poole et al. 2001). The layers of articular cartilage include the superficial tangential zone (STZ) (10-20%), middle zone (40-60%), deep zone (30%), calcified cartilage, tidemark and subchondral bone (Mandelbaum et al. 1998, Fox, Bedi & Rodeo 2009) (Figure 1). In the superficial zone, the chondrocytes are flattened and aligned parallel to the surface together with a very polarized close-knit organization of thin collagen fibers protecting the deeper layers. Chondrocyte density is lower in the middle (transitional) zone, as it contains proteoglycans and the collagen fibers are arranged obliquely and have a larger diameter. The middle zone provides functional and an anatomic bridge between the superficial and deep zones, being the first line to resist compressive forces. The deep zone contains the largest diameter collagen fibers, the highest proteoglycan content and the lowest water concentration, being responsible for providing the greatest resistance to compressive forces. The chondrocytes are arranged in columnar orientation, parallel to the collagen fibers (Poole et al. 2001, Buckwalter, Mankin & Grodzinsky 2005, Fox, Bedi & Rodeo 2009).

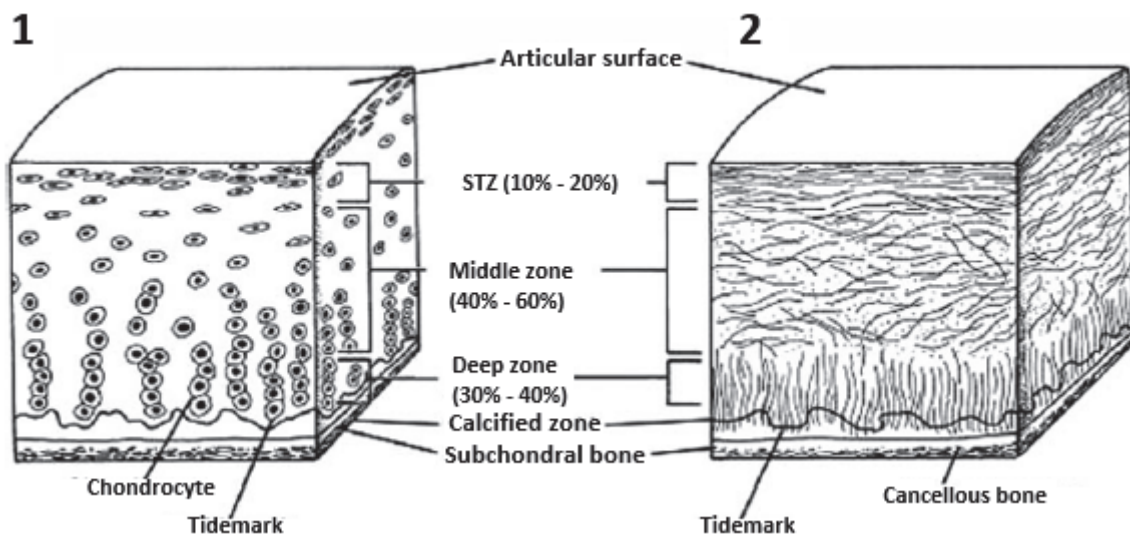


FIGURE 1 A cross-sectional diagram of healthy articular cartilage. 1: Cellular organization in the zones. 2: Collagen fiber architecture. Adapted from Buckwalter et al. 1994.

A variety of proteoglycans, such as aggrecan, which is present in the articular cartilage, are the second largest group of macromolecules in the ECM after collagen. They consist of a protein core with one or more glycosaminoglycan (GAG) chains covalently attached (Fox, Bedi & Rodeo 2009). In the articular cartilage ECM, most aggrecans associate with hyaluronic acid and link proteins, or small noncollagenous proteins to be more specific, to form proteoglycan aggregates (Figure 2). This aggrecan formation helps proteoglycans anchor within the ECM, preventing their displacement during tissue deformation (Buckwalter, Mankin & Grodzinsky 2005). GAGs form long strings of negative charges that repel one another and other negatively charged molecules. This negative charge attracts osmotically active cation ions, causing water molecules, which bind to PGs, to rush into the matrix, initially creating a swelling hydrostatic pressure

(Lu et al. 2004, Buckwalter, Mankin & Grodzinsky 2005, Fox, Bedi & Rodeo 2009).

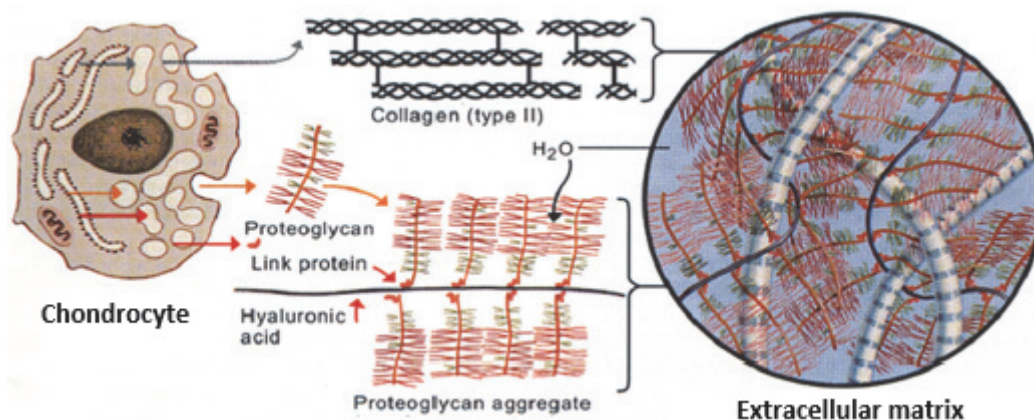


FIGURE 2 Production and structure of collagen, proteoglycans and glycosaminoglycans. Adapted from Bucwalter & Martin 1995.

Articular cartilage is subjected to a variety of dynamic and static loads. Compressive, tensile and shear forces during joint loading cause the fluid within the articular cartilage matrix move, resulting in an immediate increase in interstitial fluid pressure dampening and distributing loads within cartilage to subchondral bone. Increased pressure causes the fluid to flow out of the ECM, and when the compressive loading is removed, interstitial fluid flows back into the tissue (Buckwalter, Mankin & Grodzinsky 2005, Fox, Bedi & Rodeo 2009). Nutrition of the articular cartilage takes place during this diffusion from synovial fluid. Without a direct supply of nutrients via blood vessels, chondrocytes depend primarily on anaerobic metabolism (Fox, Bedi & Rodeo 2009). Regular, cyclic loading of the joint enhances PG synthesis (making cartilage stiff), cartilage nutrition and the removal of catabolites from the cartilage. Further, cartilage that is regularly subjected to high levels of stress shows a higher cell volume, higher content of PGs and is stiffer (Arokoski et al. 2000), whereas inactivity of the joint has been shown to lead to the degradation of cartilage (Buckwalter & Mankin 1998). Also, abnormal loading or cartilage related injury may compromise this metabolism equilibrium and lead to the loss of articular cartilage, its biochemical properties and normal function, leading to the clinical syndrome of OA (Arokoski et al. 2000, Buckwalter, Mankin & Grodzinsky 2005).

Age determines the composition of ECM, and even though the total number of chondrocytes remains essentially unchanged, aging causes zonal changes in the distribution of chondrocytes. In the superficial zone, chondrocytes start to dissipate, whereas an increase can be observed in the deeper layers (Fox, Bedi & Rodeo 2009, Loeser et al. 2012). The aging of articular cartilage may lead to cartilage degeneration, including the fraying, i.e. surface fibrillation, and the softening of the articular surface (Martin & Buckwalter 2002). Aging also decreases hydration, tensile strength and the stiffness of the matrix, with a corresponding

increase in compressive stiffness. This may affect subchondral bone, which may be directed with higher forces as cartilage loses its ability to undergo reversible deformation, increasing the risk of joint degeneration (Martin & Buckwalter 2002, Buckwalter, Mankin & Grodzinsky 2005, Fox, Bedi & Rodeo 2009). Also, during aging, the tidemark separating calcified from non-calcified cartilage duplicates itself and moves towards the articular surface. Therefore, the consequent thinner rim of non-calcified cartilage leads to increased shear stress, and thus, increased cartilage vulnerability (Felson & Zhang 1998). Furthermore, decreased cell function, the size and aggregation of proteoglycan aggrecans, the ability of chondrocytes to maintain and repair the tissue, responsiveness to anabolic growth factors and less functional link proteins are all related to aging (Martin & Buckwalter 2002).

2.1.3 Definition of knee OA

Osteoarthritis is a whole organ disease that develops slowly over 10-15 years, affecting individuals' activities of daily living and the ability to work (Wieland et al. 2005, Roos & Arden 2016). OA has been often referred to as the most common degenerative joint disease which causes pain and disability (Loeser et al. 2012). Additional characteristics of OA are the remodeling of subchondral bone, osteophyte formation, ligamentous laxity, periarticular muscle weakness, meniscal damage and synovial inflammation (Bennell & Hinman 2011, Litwic et al. 2013, Roos & Arden 2016). OA has a direct correlation to age, i.e. aging increases the risk of OA (Martin & Buckwalter 2002). Aging itself does not cause OA, but the age-related metabolic and phenotypic decline of chondrocytes increases articular cartilage degeneration risk and limits cells ability to repair the tissue once degenerative changes occur (Martin & Buckwalter 2002).

Defining knee OA has shown to be problematic, as in most OA research, the disease has been defined by radiography without considering other structural findings and the symptoms experienced by the patient. It has been shown that up to 50% of patients with radiographic knee OA do not experience regular pain and up to 50% of patients with knee pain suggestive of OA do not have the radiographic features of OA (Wieland et al. 2005, Litwic et al. 2013, Roos & Arden 2016). Thus, knee OA can be defined as radiological, clinical or subjective. The radiological definition is most widely assessed using the 0-4 Kellgren & Lawrence score, in which the severity of knee OA is related to the presumed appearance of osteophytes, joint space loss, cysts and sclerosis (Kellgren & Lawrence 1957) (Table 1). Clinical knee OA is defined by finding features from examination and the history of the patient using standards and criteria for diagnosis such as the American College of Rheumatology (ACR) criteria (Altman et al. 1986). Subjective OA relies on the assessment of the patient and whether the disease is present or not (Litwic et al. 2013).

TABLE 1 Radiographic OA classification according to the Kellgren-Lawrence grading system (Kellgren & Lawrence 1957).

Grade	Description
0	No changes
I	Doubtful narrowing of the joint space and possible osteophytic lipping
II	Definite osteophytes and possible narrowing of the joint space
III	Moderate multiple osteophytes. Definite narrowing of joint space, some sclerosis, and possible deformity of the bone ends
IV	Large osteophytes, marked narrowing of the joint space, severe sclerosis, and definite deformity of the bone ends

In summary, the association between structural signs and symptoms is essential when defining OA, as symptomatic OA is influenced by comorbidities, pain processing factors and other personal traits (Javaid et al. 2012, Roos & Arden 2016) (Table 2).

TABLE 2 Summary of knee OA symptoms, clinical and radiological findings.

Symptoms	Clinical findings	Radiological findings
Pain	Reduced knee ROM	Joint Space narrowing
Joint stiffness in morning	Malposition	Osteophytes
Reduced knee ROM	Painful stability tests	Subchondral sclerosis
Reduced functional capacity	Swelling	Bone cysts
	Muscle weakness	Bone end deformities
	Crepitus	

2.1.4 Magnetic resonance imaging in knee OA

Noninvasive imaging techniques are important tools for monitoring articular cartilage or whether knee OA diagnosis needs to be confirmed (Fox, Bedi & Rodeo 2009). Conventional radiography predominantly reveals the bony and joint-space-related changes in the knee joint, whereas different MRI methods can in addition visualize all the structures within the knee joint and subchondral cancellous bone as well as the structural pathology associated with pain (Hunter et al. 2015). MRI is superior to radiography because of its superior soft tissue contrast and multiplanar capabilities and because it requires no exposure to ionizing radiation (Fox, Bedi & Rodeo 2009, Hunter et al. 2015). Different MRI techniques can be used for the semi-quantitative evaluation of cartilage morphology, primarily when diagnosing focal lesions and tissue volume (clinical purposes) and for cartilage quality studies using quantitative mapping that is sensitive to the biochemical and structural changes in the ECM that precede visible changes in cartilage (research purposes). Techniques that usually have been applied in clinical trials include T1 and T2-weighted image mapping with fast spin-echo-based sequences (Bashir et al. 1999, Hunter et al. 2015). However, it has been

shown that MRI-assessed cartilage measures do not discriminate mild radiographic (K/L ratings 0/I/II) OA severity (Multanen et al. 2015).

Nondestructive visualization techniques for the distribution of functionally important macromolecules in living cartilage have been under development during the last couple of decades. One promising approach has been proton-based delayed gadolinium enhanced MRI of cartilage (dGEMRIC) for measuring the estimated GAG content of articular cartilage (Bashir et al. 1999, Nieminen et al. 2002, Burstein & Gray 2003). This approach involves the intravenous injection of a negatively charged MRI contrast agent, gadolinium, embedded in diethylene triamino pentaacetic acid (Gd DTPA²⁻). With appropriate doses, gadolinium will distribute in a higher concentration in areas that are depleted in GAG and will be excluded from areas which have high GAG concentration (i.e. lower concentrations of negatively charged GAG chains lead to higher contrast agent distribution due to the ionic properties of Gd DTPA²⁻) (Bashir et al. 1999, Burstein & Gray 2003, Lammentausta et al. 2006). Gadolinium reduces the T1 relaxation time and has a concentration-dependent effect on the dGEMRIC, thus the images in the presence of gadolinium reflect the GAG concentration of the articular cartilage (Bashir et al. 1999, Dahlberg et al. 2012).

T2-weighted images are directly related to the cartilage collagen content, integrity of the collagen network in the ECM and fiber orientation (Fragonas et al. 1998, Nieminen et al. 2000, Nieminen et al. 2001). T2 mapping has also been shown to be feasible to reflect the mechanical properties of articular cartilage at clinical MRI field strength, i.e. 1.5 Tesla (Lammentausta et al. 2006), and it has been shown to correlate with loading, i.e. thicker cartilage was correlated with higher condylar loading during walking (Van Rossom et al. 2017). Furthermore, T2 values are associated with the disease development of radiographic knee OA (Dunn et al. 2004). However, these MR parameters are not unambiguous indicators for estimated cartilage quality due to their low response to PG depletion and thus T2 imaging alone may not be suitable for a complete characterization of articular cartilage condition (Nieminen et al. 2000).

In summary, combining different MRI methods, such as dGEMRIC, which is sensitive to the cartilage GAG content and T2 mapping, which is sensitive to the properties of the collagen network, may give more in-depth analysis on the structural and functional integrity of articular cartilage. However, these methods are challenged by several issues, such as long imaging times, the significant delay between contrast agent injection and imaging, the susceptibility to motion and pulsating artefacts and contrast agent dosing bias in obese/overweight subjects (Dahlberg et al. 2012).

2.1.5 Symptoms and signs

OA may develop in any joint, but knee is the most commonly affected location for the disease (Litwic et al. 2013). Most common early symptoms for knee OA are pain, stiffness, swelling and limited functional capacity (affecting e.g. the ability to walk the stairs and get in and out of the car) and reduced knee range

of motion. Pain might get worse during physical activities but alleviate during rest, and as the disease advances, pain might occur during rest and the night. An increase in knee pain over the period of three years has been found to be associated with an increase in activity limitations. This result emphasizes the important role of knee pain in the development of activity limitations in early knee OA (van der Esch et al. 2014). Chronic pain in OA depends primarily on the activation of sensory neurons that innervate the knee joint. All joint tissues, except cartilage, including subchondral bone and synovium are densely supplied by small-diameter nociceptive neurons and neuronal sensitization is an important feature in OA pain (Wieland et al. 2005, Lohmander et al. 2007). Also, central pain sensitization may occur, and psychosocial factors are important determinants of pain severity in OA (Lohmander et al. 2007).

OA affects the whole joint, not just the articular cartilage but also the subchondral bone, ligaments, menisci, joint capsule, synovium and the surrounding musculature (Figure 3). Further, OA symptoms may lead to impaired performance in the workplace, and 25% of the patients cannot perform their main activities of daily living, often leading to depression and social isolation (Hunter & Felson 2006, Wieland et al. 2005, Bennell et al. 2011).

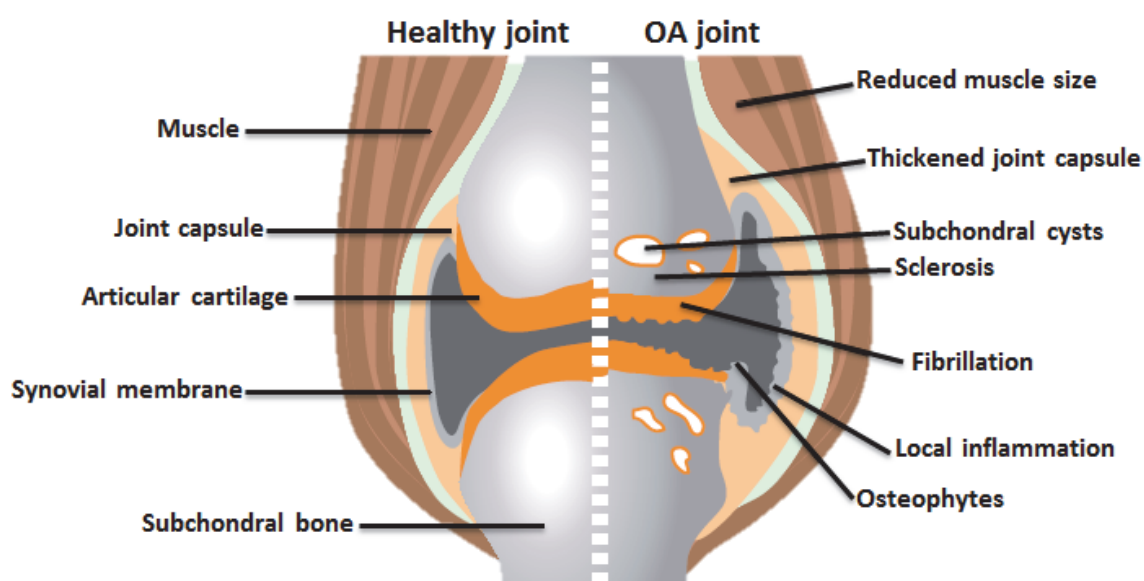


FIGURE 3 Healthy and osteoarthritic knee joint. Reproduced and adapted with permission from Kumppanina nivelrikko - näin tulen toimeen, Suomen Nivelyhdistys ry.

In OA, cartilage homeostasis, i.e. the balance between synthesis and degradation of matrix components, is compromised as matrix degradation outpaces its synthesis. As cartilage degenerates, its surface starts to fibrillate, changes in the subchondral bone, such as sclerosis, cysts, thickening and osteophytes can be observed and also cause crepitus, synovium becomes inflamed, joint space narrows down and reduction in surrounding musculature size can be observed (Bennell et al. 2011). The International Classification of Functioning, Disability

and Health (ICF) represent a broad view of functioning and disability across all domains of functioning in daily life. ICF framework can be used to represent the wide range of factors that are related to the progression of knee OA. Figure 4 summarizes the screening of knee OA using ICF framework.

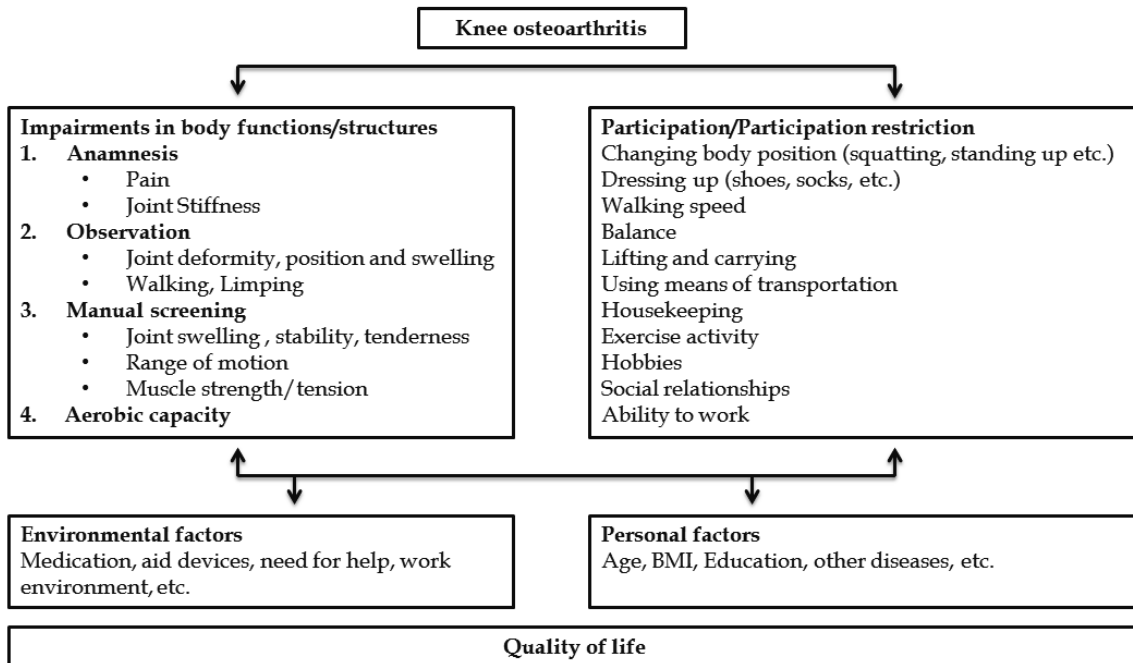


FIGURE 4 Screening of knee OA using ICF framework. Adapted (Polven ja lonkan nivelrikon fysioterapia 2013).

2.1.6 Pathogenesis of knee osteoarthritis

Cartilage matrix is continually being turned over as degraded matrix molecules are replaced by newly synthesized molecules (Dahlberg et al. 2012). Alteration or disruption of the molecular structure and composition of the matrix are among the first events to occur in articular cartilage degeneration. Other early degenerative changes include surface fibrillation of articular cartilage, superficial fissures, sclerosis (thickening) of subchondral bone and disruption of matrix-molecular framework (decreased proteoglycan content and increased water content). As a result of cartilage breakdown, the synovium becomes inflamed. Damage to the tissue stimulates a chondrocytic synthetic and proliferative response that maintains or even restores the articular cartilage. However, in instances of progressive cartilage degeneration, the chondrocytic anabolic response eventually declines and the imbalances between degradative activity and chondrocyte synthesis lead to the progressive thinning of articular cartilage (Buckwalter & Martin 1995, Buckwalter 2002, Wieland et al. 2005). Further, a loss of matrix proteoglycans increases the permeability of articular cartilage and decreases its stiffness. Also, minimal joint space narrowing can be observed.

These changes may cause a greater loading of the remaining macromolecular framework, including the collagen fibers, increasing the vulnerability of the tissue to additional damage from loading which in part can cause swelling of the matrix and injure chondrocytes (Buckwalter 2002). Furthermore, a change in the homeostasis of anabolic versus catabolic processes can cause a net catabolic increase and thus cartilage degeneration. Many knee OA patients also experience muscle atrophy in the surrounding muscles of the involved joint, in particular in the quadriceps muscle (Buckwalter & Martin 1995, Buckwalter 2002, Wieland et al. 2005, Dahlberg et al. 2012).

As OA advances, fibrillated cartilage comes off into joint space, fissures penetrate the subchondral bone and the sclerosis of subchondral bone is pronounced. Enzymatic degradation and thinning of articular cartilage is present, joint space is narrowing, bone starts to remodel and osteophytes start to form (Buckwalter & Martin 1995). It has been discussed whether osteophytes can help stabilize the joint and redistribute forces to protect the cartilage (Brandt 1999). However, it has been shown that cartilage degeneration positively correlates with osteophyte formation, osteophytes limit knee ROM and that osteophyte formation is more closely associated with pain than the joint space narrowing (Lanyon et al. 1998).

In the end-stage of knee OA, the articular surface of subchondral bone is exposed (bone-on-bone articular surface), subchondral bone has altered (imbedded cartilage, cysts and sclerosis) and bone shows remodeling osteophytes (Buckwalter & Martin 1995, Buckwalter 2002, Wieland et al. 2005). Figure 5 shows the etiopathogenesis hypothesis of the early loss of GAG and collagen in OA.

Pathologic changes in menisci are common among people with knee OA (Loeser et al. 2012). The key functions of menisci are to transfer weight, reduce the compressive load in tibiofemoral joint and ensure the joint lubrication, proprioception and stabilization (Englund et al. 2008, Englund, Guermazi & Lohmander 2009). It has been shown that meniscal damage occurs in 63% of the adults with radiographically confirmed symptomatic (knee pain or stiffness on most days) knee OA and in 60% of those without these symptoms (Englund et al. 2008). The relationship between knee OA and meniscal damage is complex as a meniscal lesion in a healthy knee can lead to knee OA as a result of the loss of meniscal function, but knee OA may also lead to meniscal tears which can accelerate the disease process (Englund, Guermazi & Lohmander 2009). Furthermore, an increase in vascular penetration together with increased sensory nerve densities has been noted in OA menisci, making menisci serve as a possible source of pain in knee OA (Loeser et al. 2012).

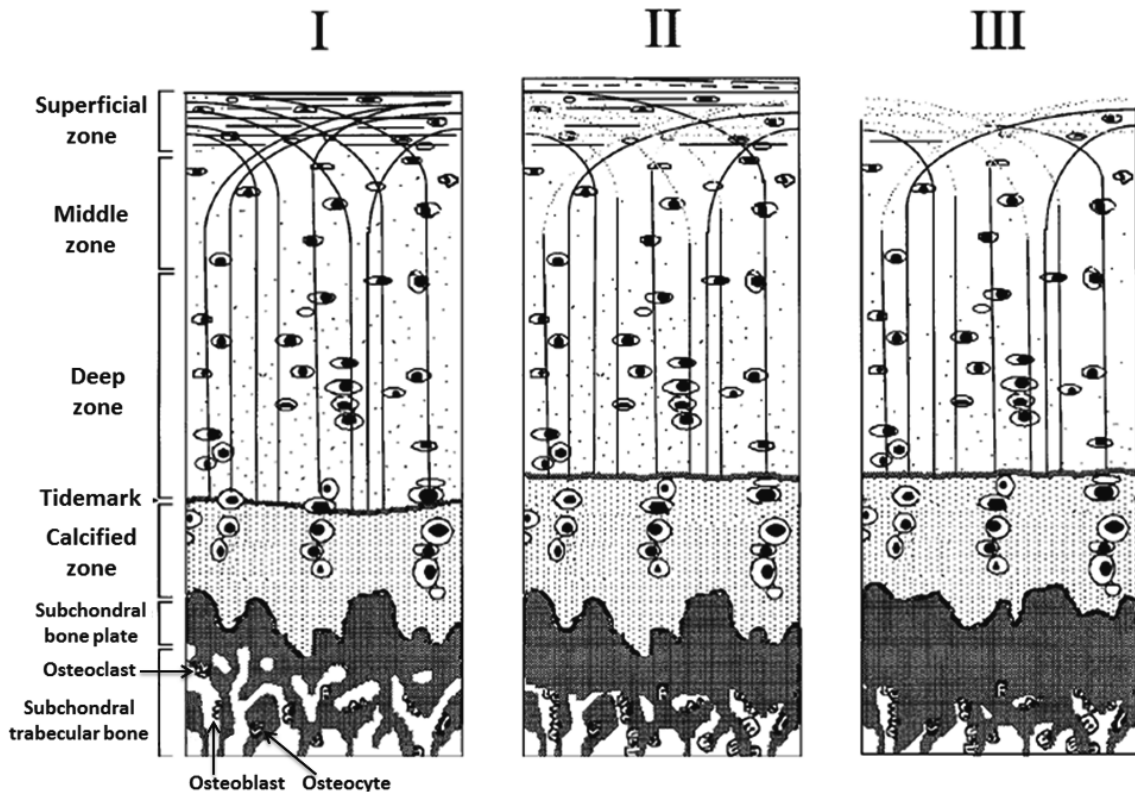


FIGURE 5 Etiopathogenesis of OA in a beagle dog model. Oval structures represent chondrocytes, dots GAGs and curved lines collagen fibers. I: Normal histology of intact articular surface. II: Depletion of GAGs in superficial and intermediate zones with disorganization of the superficial zone collagen network and thickening and softening of cartilage. Simultaneously, calcified cartilage and subchondral bone plate grow thicker. III: Further loss of GAGs, fibrillation of cartilage surface and progression of subchondral bone sclerosis. Adapted from Arokoski et al. 2000).

2.1.7 Risk factors

OA is a heterogeneous disease with a large number of risk factors that often interact with each other (Roos & Arden 2016) (Figure 6). These complex multifactorial processes take decades to develop. This is caused by aberrant local biomechanical factors acting within the context of systemic susceptibility (Felson & Zhang 1998, Hunter & Felson 2006, Bennell et al. 2011, Roos & Arden 2016). Systemic factors operate by making cartilage more vulnerable to injuries, by directing damage to joint tissue or by impairing the repair process in damaged joint tissue, thus increasing the risk for OA (Felson & Zhang 1998, Hunter & Felson 2006, Litwic et al. 2013). Once systemic vulnerability factors are in place, local biomechanical factors, such as muscle weakness, misalignment or altered structural environment of the joint such as meniscal damage, facilitate the progression of the disease. Also, overweight/obesity and joint injury can affect the loading of the knee and thus increase the risk of developing OA or experiencing its progression (Hunter & Felson 2006). This dissertation will focus

on the following risk factors: Age, gender, obesity, muscle strength, joint instability, knee injury and loading (physical activity/occupation).

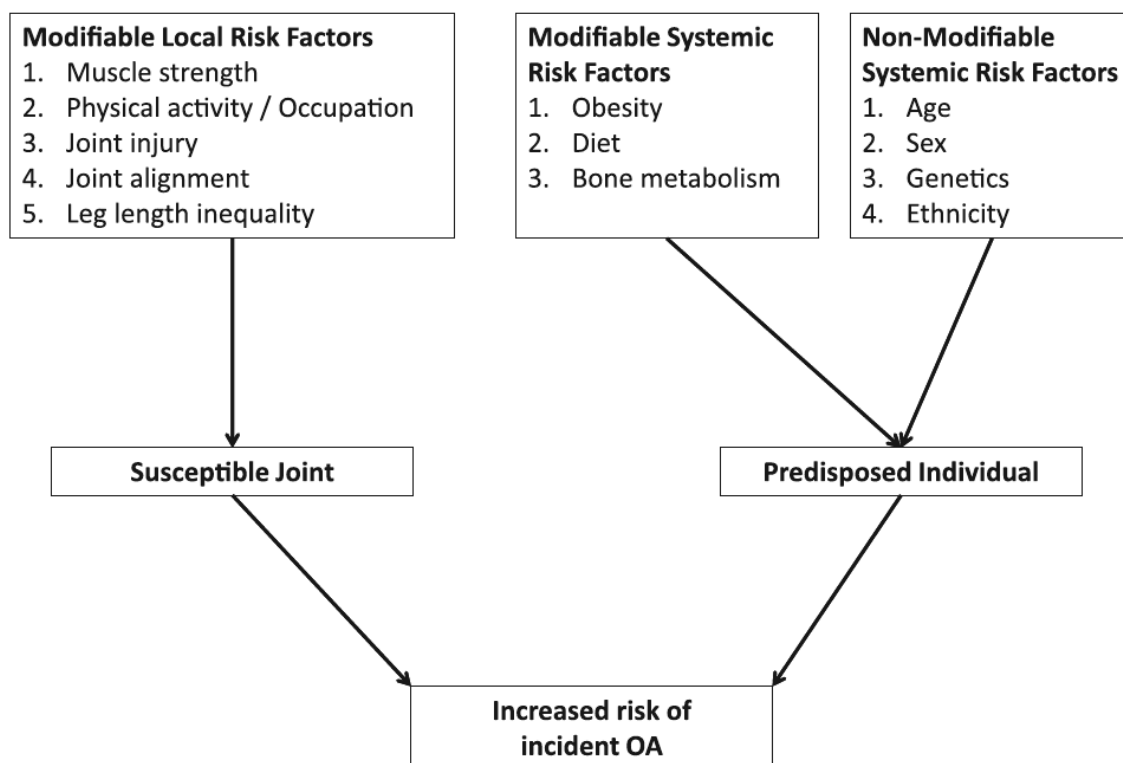


FIGURE 6 Potential risk factors for susceptibility to OA incidence. Reproduced with permission from Johnson & Hunter 2014.

Age and gender

Aging itself is not necessarily a risk factor for OA, whereas age-related changes in bodily structures and loading patterns might be. Nevertheless, the prevalence and incidence of radiographic and symptomatic OA in all joints are strongly correlated with age (Felson & Zhang 1998, Litwic et al. 2013, Silverwood et al. 2015). Age-related increase in the prevalence and incidence of OA is likely due to several biologic changes that occur with aging, including a decreased responsiveness of chondrocytes to growth factors (decreased cartilage repair), an increase in the laxity of ligaments surrounding the joints (unstable joints and joints that are more susceptible to injury) and a failure of structures and proprioception protecting joints, (e.g. weakened muscles and slowed peripheral neurologic responses) (Felson & Zhang 1998, Johnson & Hunter 2014). All these factors together result in a decline in functional capacity. The aging of articular cartilage has been discussed earlier.

Men have a higher prevalence and incidence of OA before the age of 50, but after 50, women's prevalence and incidence for the disease increases dramatically (Felson & Zhang 1998). Also, women tend to have more severe knee OA, particularly after menopausal age (Srikanth et al. 2005). It has been hy-

pothesized that hormonal factors might play a role in OA development, but the results of epidemiologic and clinical studies are controversial (Spector et al. 1997, Cirillo et al. 2006, de Klerk et al. 2009). Some studies have shown protective effect for hormone or oestrogen on progression to joint replacement (Cirillo et al. 2006) or on radiographic knee and hip OA (Spector et al. 1997). On the other hand, it was shown in systematic review from de Klerk et al. that there was no clear association between gender hormones and radiographic knee, hip or hand OA (de Klerk et al. 2009). Differences between genders may also be caused by differences in bone strength, alignment, ligament laxity, pregnancy and neuromuscular strength (Johnson & Hunter 2014). The age-related loss of cartilage and declined functional capacity together with hormonal changes put women at high risk for knee OA.

Obesity

Obesity is a major risk factor for knee OA as a strong link between obesity and the development of OA, particularly that affecting knee, has been illustrated (Litwic et al. 2013, Silverwood et al. 2015, Makaram & Clement 2016). This is true regardless of how knee OA is defined, be it through symptoms or radiograph, and irrespective of whether the focus is on the tibiofemoral or patellofemoral joint (Felson & Zhang 1998). Further, it has been demonstrated that women in the highest tertile of BMI had six times higher odds of developing knee OA and almost 18 times higher odds of developing bilateral knee OA compared with women in the lowest tertile (Hart & Spector 1993). This has been also seen in similar studies of a population of African-American and Caucasian women (Lachance et al. 2001) and of general population in Norway (Grotle et al. 2008). There are two different mechanisms for weight causing OA (Felson & Zhang 1998, Makaram & Clement 2016). First, being overweight increases the forces across the weight bearing joint (Felson & Zhang 1998). Obesity-related abnormal loads have been associated with atypical chondrocyte and cartilage functions (Makaram & Clement 2016). Second, in recent years, significant research effort has been established with respect to adipose tissue and its influence on OA (Chen et al. 2006, Gegout et al. 2008). Research has been done in particular on the involvement of leptin expressions, or adipocytokine secreting in adipose tissue, in the development of OA, as it has been shown to be actively present in synovial fluid and is now thought to directly influence joint degradation or through indirect inflammatory processes involving cartilage degeneration (Wieland et al. 2005, Vincent et al. 2012, Makaram & Clement 2016). Further, higher body weight and BMI are associated with increased leptin expression and levels, which is directly associated with greater cartilage degeneration (Dumond et al. 2003).

Muscle strength and joint instability

Lower limb muscles, especially the quadriceps, play an important role in the management of knee OA. The muscles in the knee produce movement and maintain stability, and they also have an important influence on joint loading by controlling how loads and forces are distributed within the joint (Bennell et al. 2013, Makaram & Clement 2016). Muscle weakness is an independent risk factor for the development of knee OA. Together with impaired muscle function, which is a consequence of physical inactivity, muscle weakness is commonly seen after a knee injury and is associated with knee pain when weak quadriceps are unable to provide adequate control of tibial translation during ambulation (Segal & Glass 2011, Bennell et al. 2013, Øiestad et al. 2014, Roos & Arden 2016). These impairments may also reduce the shock absorbing properties of the cartilage, impairing the ability to dissipate knee joint loads and thus increasing contact stress (Segal & Glass 2011). Therefore greater dynamic loads result in the progressive degeneration of knee articular cartilage (Makaram & Clement 2016), whereas greater quadriceps muscle strength in women is associated with a lower risk for cartilage loss and progression of tibiofemoral joint space narrowing (Segal & Glass 2011). It is possible that knee OA itself or OA-related chronic pain will lead to quadriceps weakness due to disuse atrophy, thus it is unclear whether muscle weakness is a cause or consequence of knee OA (Wieland et al. 2005, Litwic et al. 2013). Furthermore, in early OA patients, decreased muscle strength is associated with an increase of activity avoidance because patient minimizes the use of the painful limb (van der Esch et al. 2014).

Lower muscle strength has been associated with the presence of self-reported knee instability (Knoop et al. 2012), and majority of OA patients report knee instability (Fitzgerald, Piva & Irrgang 2004, Knoop et al. 2012). Knee instability has demonstrated as buckling, shifting or giving way of the knee during the activities of daily living (Fitzgerald, Piva & Irrgang 2004, van der Esch et al. 2012). Knee instability is significantly associated with activity limitations, in addition to knee pain and muscle strength, and thus should be addressed together with muscle weakness in clinical assessment and targeted for therapeutic interventions (van der Esch et al. 2012).

Knee injury

In theory, joint damage can occur either through sudden major injury or stereotyped repetitive activity that exceeds the ability of muscles and tendons to withstand such use, thus transmitting force to cartilage (Felson & Zhang 1998, Buckwalter 2002). It has been shown that those with previous traumatic knee injury are at higher risk for the onset of knee OA (Litwic et al. 2013, Silverwood et al. 2015). In many patients, acute injuries occur simultaneously with injuries to other tissues, including cruciate and meniscal tears, fractures and dislocations, which can lead to increased risk of knee OA and musculoskeletal symptoms (Buckwalter 2002, Litwic et al. 2013). Major injuries often lead to altered

biomechanics, causing increased impulsive or shear stress on local cartilage areas, which may induce progressive changes associated with cartilage (Felson & Zhang 1998). Especially two specific types of major knee injuries have been strongly associated with subsequent knee OA: meniscal tears and anterior cruciate ligament (ACL) damage (Felson & Zhang 1998, van Meer et al. 2015). OA development in the injured joints is caused by intra-articular pathogenic processes initiated at the time of injury, together with long-term changes in dynamic joint loading (Lohmander et al. 2007).

In a longitudinal study by Englund et al., it was shown that 50-79 year-old women and men with significant meniscal damage (versus no meniscal damage) had an odds ratio of 7.4 for the development of tibiofemoral OA 30 months after the incidence (Englund et al. 2009). A partial or full removal of the meniscus leads to increased joint cartilage strain under static loading and to increased dynamic deformation in knee joint areas known to develop post-meniscectomy OA as the central load bearing cartilage region remains chronically deformed and dehydrated even after the cessation of loading (Song et al. 2006, Song et al. 2008, Englund, Guermazi & Lohmander 2009).

OA is a long-term complication of ACL rupture (van Meer et al. 2015). ACL rupture affects the kinematics of the knee, such as the anterior displacement of tibia resulting in shear forces being applied mainly on the medial side of the knee. Thus, increased shear forces on articular surface lead to a loss of articular cartilage. At the same time the posterior horn of the medial meniscus becomes wedged between the posterior condyle of the femur and the tibia, resulting in longitudinal splints and leading to medial meniscal tear if left untreated for ten years (Lohmander et al. 2007, Louboutin et al. 2008). Secondly, the origin of ruptured ACL induced knee OA might be due to knee instability and giving away, i.e. the stretching of the peripheral ligamentous structures, and injury-related alterations in the biomechanics caused by shearing forces affecting the articular cartilage (Louboutin et al. 2008). Furthermore, a substantial force is required to tear a healthy ACL. Injured knee joint cartilage will have sustained a considerable mechanical impact, which in itself can lead to disruption of the cartilage matrix, chondrocyte death and changes in cell metabolism, which are associated with OA development (Buckwalter 2002).

Prevalence for painful and functional impairment-related knee OA of both ACL and menisci injury is 50% at 10-20 years after the diagnosis (Lohmander et al. 2007). Injuries to menisci (patient mean age around 35 years) and ACL (patients often younger than 30 years) often occur in athletes and physically active, young, healthy population causing a phenomenon described as "young patients with old knees". Symptomatic OA in this young population remains a largely unsolved treatment challenge as there is insufficient evidence to prove that surgical treatment of ACL or meniscus lesions is able to diminish the future development of knee OA (Lohmander et al. 2007, van Meer et al. 2015).

Daily physical loading and joint alignment

Articular surface injuries depend on how loads and the rate of loading affect articular cartilage. Slowly and suddenly applied loads differ considerably in their effect. Slowly applied loads allow the cartilage to deform and decrease the force applied to the matrix framework through fluid movement whereas with rapid and sudden impact or the torsional joint loading of the joint surface, the matrix framework sustains greater a force. If this force is great enough, it ruptures the matrix macromolecular framework, damages the cells and exceeds the ability of the cartilage to prevent subchondral bone damage by distributing and dampening loads (Buckwalter 2002). Further, there is no evidence of a causal link between the estimates of structural progression of knee OA and knee joint loading during walking (Henriksen et al. 2014). According to a recent meta-analysis, results on the role of running in knee OA are conflicting and it is impossible to determine the actual role of running (Timmins et al. 2017), although it has been previously proposed that elite runners appear to be at an increased risk of knee OA in later life (Felson & Zhang 1998).

Radiographic imaging routinely shows that joint space narrowing is present to a greater extent in the medial compartment versus the lateral compartment. This has been found to be due to knee malalignment that places the knee joint into a varus position, thus increasing loading on the medial side of the joint (Vincent et al. 2012). During walking, 60-80% of the load passes through the medial tibiofemoral compartment in healthy knees, making it more vulnerable to factors that increase load across the knee (Dayal et al. 2005). Peak knee adduction moment (M_{add}) describes this load across the medial and lateral tibial plateaus. As degeneration of the knee joint cartilage during OA progresses, an increase in varus malalignment can be observed causing increased M_{add} (Vincent et al. 2012). Thus, increased M_{add} has been associated with the progression and possibly the initiation of knee OA (Andriacchi, Koo & Scanlan 2009). Further, medial and lateral femoral condyles are both shaped like cams, but the two tibial surfaces these condyles are in contact with are shaped differently (Vincent et al. 2012). When exposed to loading, the medial femoral condyle will experience increased contact with the concave tibial surface when comparing with the lateral condyle that will experience less contact with the convex tibial facet (Andriacchi et al. 2006). Repetitive exposure of the thinner medial cartilage to greater internal rotation will wear areas of thinnest cartilage first and possibly induce symptomatic knee OA (Vincent et al. 2012).

The risk of developing knee OA in mid-life is also shown to be two times greater in occupations that require both carrying and repetitive kneeling or squatting compared to those whose occupation did not require these physical activities (Felson & Zhang 1998, Jensen 2008, Klusmann et al. 2010, Zhang & Jordan 2010). Further, this association has been found to be much higher among subjects who were overweight and whose occupation involved lifting (Coggon et al. 2000).

2.2 Management of knee osteoarthritis

There is no known cure, treatment or drug available with proven disease-modifying efficacy in OA. Therefore, the current management of knee OA focuses on prevention and reducing the symptoms and decrease in function associated with the disease (Hunter & Felson 2006, Wieland et al. 2005, McAlindon et al. 2014, Roos & Arden 2016). Most appropriate individual management strategies - usually a combination of treatment strategies - should be identified by selecting interventions to correct or at least attenuate the risk factors of knee OA (Roos & Arden 2016). It is also known that there is considerable discordance between the symptoms and the structural signs of knee OA. Thus, the recommended non-pharmacological main aims of knee OA management according to current evidence-based clinical guidelines in early treatment are to educate patients about the disease, exercise, control pain, lose weight, improve function and alter the process of the disease and its consequences (Hunter & Felson 2006, Roos & Juhl 2012, Roos & Arden 2016). Pharmacological management (e.g. paracetamol and NSAIDs), aids (e.g. orthoses/braces) and passive treatments (e.g. physiotherapy and acupuncture) are the second line treatment whereas joint replacement surgery (e.g. arthroscopy) is the third and final line for joint failure (Hunter & Felson 2006, Roos & Juhl 2012, McAlindon et al. 2014) (Figure 7). These treatment lines are not hierarchical, i.e. OA treatment would progress step-by-step towards surgery, but they overlap each other as depicted in Figure 7.

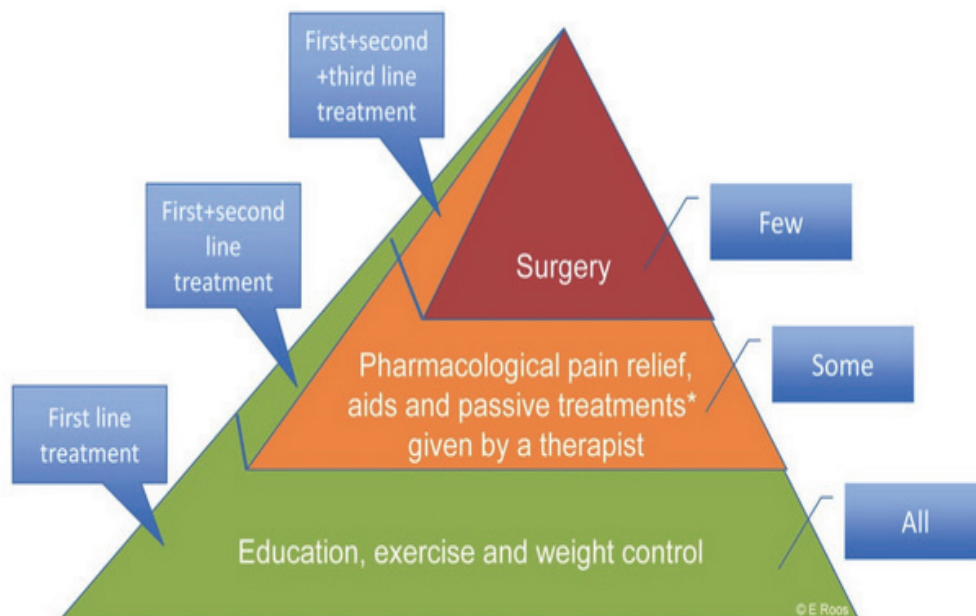


FIGURE 7 Osteoarthritis treatment pyramid. Reproduced with permission from Roos & Juhl 2012.

Prevention strategies for knee OA continuum can be separated into primary, secondary and tertiary prevention strategies. Primary prevention includes the prevention of knee injury (susceptible individuals), secondary prevention includes exercise and dietary intervention in individuals who are overweight, have impaired muscle function or prior joint injury (early disease, minor joint impairment) and tertiary prevention involves early treatment of OA to prevent the progression of the disease (late and end stage of disease, joint failure) (Felson & Zhang 1998, Roos & Arden 2016).

2.2.1 Non-pharmacological treatment

According to several international guidelines, exercise, strength training, self-management and education and weight management are the key elements for non-pharmacological treatment of knee OA (Hochberg et al. 2012, Fernandes et al. 2013, McAlindon et al. 2014, Schiphof, van den Driest & Runhaar 2018). Today, additional treatment options such as knee braces, orthoses, insoles or physical therapy (e.g. acupuncture) alone are less supported or uncertain, and the guidelines related to them are inconsistent (Bennell, Hall & Hinman 2015, Schiphof, van den Driest & Runhaar 2018). Thus, the main focus of this dissertation is on exercise interventions. There is a high level of evidence supporting the benefits of exercise in mild and moderate knee OA (Roos & Juhl 2012). Exercise is recommended for the treatment of knee OA by all current clinical guidelines (Bennell, Hall & Hinman 2015) and is shown to be an effective non-surgical method in pain reduction and improving function in OA population (Figure 8). There is high-quality evidence from 44 RCTs indicating that therapeutic land-based exercise has short term pain benefits compared to no exercise and that this benefit is sustained for at least two to six months after the cessation of treatment. There is also moderate-quality evidence of improved self-reported physical function. This benefit also remained for longer than six months. In the same study, but with 13 RCTs, a small but significant benefit of exercise on quality of life was found on short term (Fransen et al. 2015).

Even though land-based exercise has these beneficial effects on pain, self-reported physical functioning and quality of life, there is no evidence that any type of land-based exercise modality would be superior to another, and frequency, intensity and dosage varies a lot (Roddy, Zhang & Doherty 2005, Juhl et al. 2014, Fransen et al. 2015, Schiphof, van den Driest & Runhaar 2018). Actually, exercise, irrespective of modality (land- or water-based) or type (strength or aerobic), has shown to be effective in reducing the symptoms related to knee OA and decreased function (Waller et al. 2014, Fransen et al. 2015). Therefore, land- or water-based exercise therapy can vary considerably in its content and can include muscle strengthening, aerobic exercise, balance retraining and mixed training (Bennell et al. 2011). Nevertheless, it has been suggested that optimal exercise programs for knee OA should have a single aim and focus on a single type of exercise (i.e. improving aerobic capacity, muscle strength or lower extremity performance) rather than mixing several types of exercise with dif-

ferent goals (Juhl et al. 2014). Clinical trials have provided strongest evidence for the efficacy of muscle strength training, neuromuscular training and aerobic exercise in reducing pain and/or self-reported disability in knee OA (Roddy, Zhang & Doherty 2005, Multanen et al. 2014, Lange, Vanwanseele & Fiatarone Singh 2008, Tanaka et al. 2013, Juhl et al. 2014, Zacharias et al. 2014).

As mentioned earlier, patient education and weight loss are also key elements for non-pharmacological treatment of knee OA. Shortly, the aim of the patient education is to enable patients, carers and clinicians to participate jointly in the choice of OA care pathway. Educational packages, checklists and motivating factors have been developed to overcome known barriers (Roos & Arden 2016). Weight loss is an important factor in the OA treatment pathway (McAlindon et al. 2014), as a 5-unit increase in BMI has been associated with a 35% increase in the risk of knee OA (Jiang et al. 2011). Combining exercise and diet has been shown to be more efficient in order to lose weight than one of these modalities alone (Messier et al. 2013), and weight reduction may lead to improved physical function (Christensen, Astrup & Bliddal 2005).

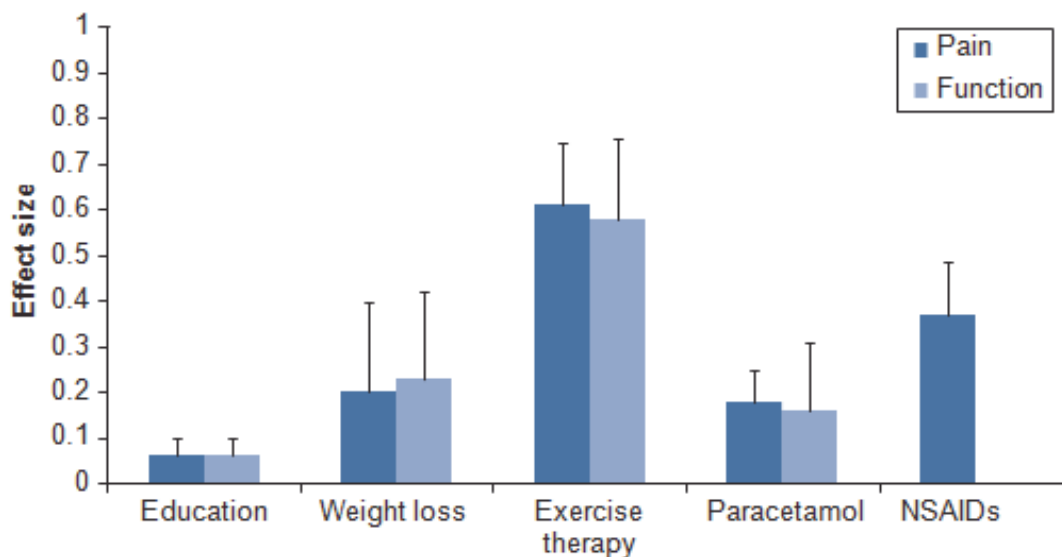


FIGURE 8 Effect sizes for the non-surgical treatment of knee OA based on meta-analyses from Juhl et al. 2014 and McAlindon et al. 2014. Adapted from Skou 2015.

2.2.2 Pharmacological treatment and surgery

Pharmaceutical agents, especially paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) play a key part in knee OA symptom control (Glyn-Jones et al. 2015). Paracetamol is a core recommendation of oral analgesic for knee OA because of its safety and efficacy for mild to moderate pain (Wieland et al. 2005, Zhang et al. 2008), but daily dose should not exceed 4g/day as paracetamol is a known liver toxin (Zhang & Jordan 2010). NSAIDs are superior to paracetamol for the relief of pain and should be considered for patients who

do not respond to paracetamol, preferably at the lowest effective dose and for the shortest duration due to the possible gastrointestinal and renal risk (Wieland et al. 2005, Bijlsma, Berenbaum & Lافeber 2011). Slow-acting drugs, such as glucosamine, chondroitin and hyaluronic acid have conflicting evidence for their effectiveness, even though some beneficial effects have been observed (Wieland et al. 2005, Bijlsma, Berenbaum & Lافeber 2011). Intra-articular injection of long-acting corticosteroids has shown to be an effective treatment of inflammatory flares of OA, but the effect starts to diminish after one week, lasting for 2-4 weeks (Wieland et al. 2005, Bellamy et al. 2005).

When conservative, non-operative treatment modalities for knee OA are no longer effective and quality of life is notably compromised, surgery could be considered (Lespasio et al. 2017). Surgical options for early knee OA include: treatment of chondral and osteochondral defects (Angele et al. 2016) and in later stages arthroscopy, osteotomies, cartilage repair and partial or total knee replacement (Lützner et al. 2009, Zhang & Jordan 2010, Rönn et al. 2011). Radiological evidence of knee OA alone does not justify surgical treatment. Patients' degree of suffering, together with radiological and clinical findings determines the time point of the possible surgery (Rönn et al. 2011). It needs to be acknowledged, that surgeries always require rehabilitation period afterwards, and it has been shown that deficits in muscle torque and power in the knee extensor muscle cross sectional area were present ten months after knee replacement, potentially causing mobility limitations, disability, limitations in negotiating stairs and risk for falls (Valtonen et al. 2009).

2.2.3 Effect of physical activity on knee articular cartilage

Daily dynamic physiological loading of the knee articular cartilage is important for the biosynthesis of various ECM molecules (Nia et al. 2013). Loading, on the other hand, as discussed earlier, may be a risk factor for developing knee OA. This interaction emphasizes the important role of biomechanics in knee OA (Bricca et al. 2017). Recent and first systematic review and meta-analysis by Bricca et al. 2017 concluded that the relationship between daily exercise dose and cartilage composition may be non-linear in healthy animals. They found inconclusive evidence for a low daily dose of exercise, possible positive effects for moderate and possible negative effects for a high daily dose of exercise on cartilage matrix composition (Bricca et al. 2017). For example, in a study comparing the response of the collagen network and GAG content of articular cartilage to physiological low dose of exercise (2.5km/day 5 days a week for 15 weeks) in young and adult guinea pigs, no significant changes between groups were observed in either of the measured variables (Hytinen et al. 2001). In a moderate dose exercise study (4km/day 5 days a week for 15 weeks) it was found that with beagle dogs running on a treadmill the GAG content was augmented by 28% (Kiviranta et al. 1988). In the same study series with beagle dogs, but with a higher dose of exercise (40km/day 5 days a week for 15 weeks), running had negative effects on both GAG content and type II collagen (Arokoski

et al. 1994). Lifelong exercise studies show that moderate, long lasting exercise (1km/day) on a treadmill accelerated the development of knee OA of C57BL mice between 2 and 18 months of age (Lapveteläinen et al. 1995), whereas the effect of long-term exercise (3 km/h, 75min/day, 5 days a week for 527 weeks while carrying jackets weighing 13% of their body weight) on canine knees showed that a lifetime of regular weight bearing exercise in healthy canines did not cause alterations in the structure and mechanical properties of articular cartilage that might lead to degeneration (Newton et al. 1997). Nevertheless, the results of the animal studies cannot be directly generalized to humans due to the differences between human and animal knee metabolism, biomechanics and loading patterns and due to the general knowledge that only 50% of findings from animal studies predict human outcomes (Perel et al. 2006, Bricca et al. 2017).

As discussed earlier in more detail, different MRI techniques have been developed for semi-quantitative evaluation of human cartilage morphology (Bashir et al. 1999, Hunter et al. 2015). Physically active lifestyle together with exercise has been shown to be beneficial for the maintenance of the biomechanical properties of cartilage in healthy humans (Tiderius et al. 2004, Wijayaratne et al. 2008, Teichtahl et al. 2009, Van Ginckel et al. 2010). Tiderius et al. (2004) found in a cross-sectional study that human knee cartilage in physically active individuals adapts to exercise by increasing the GAG content when compared to sedentary. Teichtahl et al. (2009) observed that vigorous physical activity over two years is beneficial (associated with a reduced annual rate of patella cartilage loss) to patellofemoral joints for people without pre-existing cartilage damage. This is also supported by a cross-sectional study showing that participation in exercise among middle-aged women tends to be associated with a reduction of patella cartilage loss (Wijayaratne et al. 2008). However, in a longitudinal study, Cotofana et al. (2010) did not observe any evidence that three months of strength or endurance training in untrained middle-aged women would alter tibiofemoral or patellar knee joint cartilage thickness or volume (Cotofana et al. 2010). Further, Van Ginckel et al. (2010) showed in another a longitudinal study that dGEMRIC indices in healthy young female novice runners were improved after a 10-week moderate running program (three times a week for 5km or 30min) compared to a sedentary control group. Therefore, physically active lifestyle can be effective for the maintenance of human cartilage health.

So far there are only few RCTs investigating the immediate posttreatment effects of exercise interventions on human cartilage, but they have shown that the loading created by land-based exercise interventions can improve the estimated biochemical composition of tibiofemoral (Roos & Dahlberg 2005) and patellofemoral (Koli et al. 2015) cartilage. Roos and Dahlberg (2005) found that moderate neuromuscular exercise (three times a week for four months), in patients at risk for knee OA, caused a positive change in the estimated GAG content of tibiofemoral cartilage compared to controls. Only two RCTs have investigated the effects of land-based exercise on the biochemical composition of cartilage in postmenopausal women with mild knee OA (Multanen et al. 2014, Koli

et al. 2015). Koli et al. (2015) found an improvement in the collagen matrix in the patella cartilage of women with mild knee OA following a 1-year, three times a week, high-impact exercise intervention while Multanen et al. (2014) did not see any worsening or improvement in the collagen matrix or GAG concentration of the tibiofemoral cartilage in the same study. In addition to positive cartilage responses observed in these studies (Roos & Dahlberg 2005, Koli et al. 2015), impact (Multanen et al. 2014, Koli et al. 2015) and neuromuscular (Roos & Dahlberg 2005) exercises are shown not to be harmful for the estimated biochemical composition of the knee articular cartilage in population with mild knee OA (Multanen et al. 2014, Koli et al. 2015) or at high risk of developing knee OA (Roos & Dahlberg 2005). Also, exercise is well tolerated in these populations (Roos & Dahlberg 2005, Multanen et al. 2014, Koli et al. 2015). Therefore, there is sufficient evidence to show that human cartilage has potential to adapt to loading change and that cartilage health is maintained by appropriate mechanical stimulus and environment (Teichtahl et al. 2009, Wang et al. 2013).

2.2.4 Therapeutic aquatic exercise

Therapeutic aquatic exercise (TAE) is considered one of the most central elements in the current non-pharmacological recommendations in the management of knee OA together with land-based exercise and weight loss (Zhang & Jordan 2010, Hochberg et al. 2012). Pain, which is one of the most common symptoms of knee OA, is also hypothesized to lead activity avoidance in people with knee OA, and thus also causing muscle weakness and activity limitations (e.g. instability of knee) (Holla et al. 2014). Water as an exercise environment on the other hand allows people with lower limb OA to train safely and comfortably at high intensities utilizing full joint range of motions (Roper, Bressel & Tillman 2013). Several systematic reviews have concluded that TAE has positive effects on pain, physical function and quality of life (Waller et al. 2014, Lu et al. 2015, Bartels et al. 2016).

Outcomes of aquatic exercise appear to be comparable to land-based exercises (Batterham, Heywood & Keating 2011). Therapeutic aquatic exercise offers several benefits over land-based exercise for osteoarthritic population because of the reduced loading across joints affected by pain due to buoyancy (Waller et al. 2014, Hinman, Heywood & Day 2007, Heywood et al. 2016). Water turbulence enables a method of increasing resistance (Hinman, Heywood & Day 2007) and due to the up-thrust of the water, a percentage of body weight can be decreased in proportion to the depth of immersion (Harrison, Hillman & Bulstrode 1992). Pressure and warmth of the water can further assist with pain relief, reduction of swelling and ease of movement (Hinman, Heywood & Day 2007). Although unproven, the reduced loading created by water has been thought to protect joints from further damage and allow more efficient training for populations who are unable to train effectively on land (Waller et al. 2014). Nevertheless, as with land-based exercises, there is no known superior exercise protocol of TAE, be it aerobic or strength training that would be more effective

than another in the management of knee OA (Bennell et al. 2011). However, one promising TAE modality for knee OA could be progressive aquatic resistance training that can be achieved by using different sizes of resistance equipment that increases the surface area and shape of the limb (Pöyhönen et al. 2000). It has been shown that in healthy women wearing large resistive boots, the mean of the peak drag value in knee extension was $145 \pm 30\text{N}$, whereas in barefoot conditions it was $45 \pm 15\text{N}$. The corresponding values in knee flexion were $137 \pm 26\text{N}$ with large resistive boot and $55 \pm 13\text{N}$ barefoot (Pöyhönen et al. 2001). This highlights the importance of resistive equipment during therapeutic aquatic exercise. Moreover, it has been shown that progressive aquatic resistance training program has significant benefits for physical functioning in healthy women (Pöyhönen et al. 2002) and following knee arthroplasty (Valtonen et al. 2010). Regular cyclic movements of the knee during TAE may provide sufficient mechanical stimulus and facilitate improved exchange of nutrients, thus increasing chondrocyte activity (Arokoski et al. 2000, Wang et al. 2013).

2.3 Summary of the literature

As there is no known treatment or cure that reverses or prevents the biochemical changes in the knee articular cartilage, the current management of knee OA focuses on reducing the symptoms and decreased function associated with the disease (McAlindon et al. 2014). Exercise has been shown to be effective in achieving these aims, causing positive effects on cartilage, lifestyle, systemic metabolism, the mechanical loading of the joint and psychological factors (Figure 9). Nevertheless, to our current knowledge there is no superior exercise training modality (water or land) or type (strength or aerobic) to achieve the aims of knee OA management (Waller et al. 2014, Fransen et al. 2015). Moreover, active lifestyle with participation in exercise has shown that physical activity has beneficial effects on cartilage quality in animals (Bricca et al. 2017), in healthy human population (Tiderius et al. 2004, Wijayaratne et al. 2008, Teichtahl et al. 2009, Van Ginckel et al. 2010), in people under risk of knee OA (Roos & Dahlberg 2005) and in postmenopausal women with mild knee OA (Koli et al. 2015). Unfortunately, the effects of exercise on pain are lost six months after the cessation of the training, whereas small but significant improvements in self-reported physical function are sustained up to 24 months (Fransen et al. 2015). Currently, the literature investigating the effects of exercise interventions on degenerated human cartilage is sparse, and there are no RCTs showing the long-term effects (follow-up periods after the cessation of the training) of therapeutic exercise on the biochemical composition of knee articular cartilage. Different exercise modalities (land and water) and types (strength or aerobic) together with leisure time physical activity should be investigated in order to achieve improved knowledge of the role of physical activity in knee OA management.

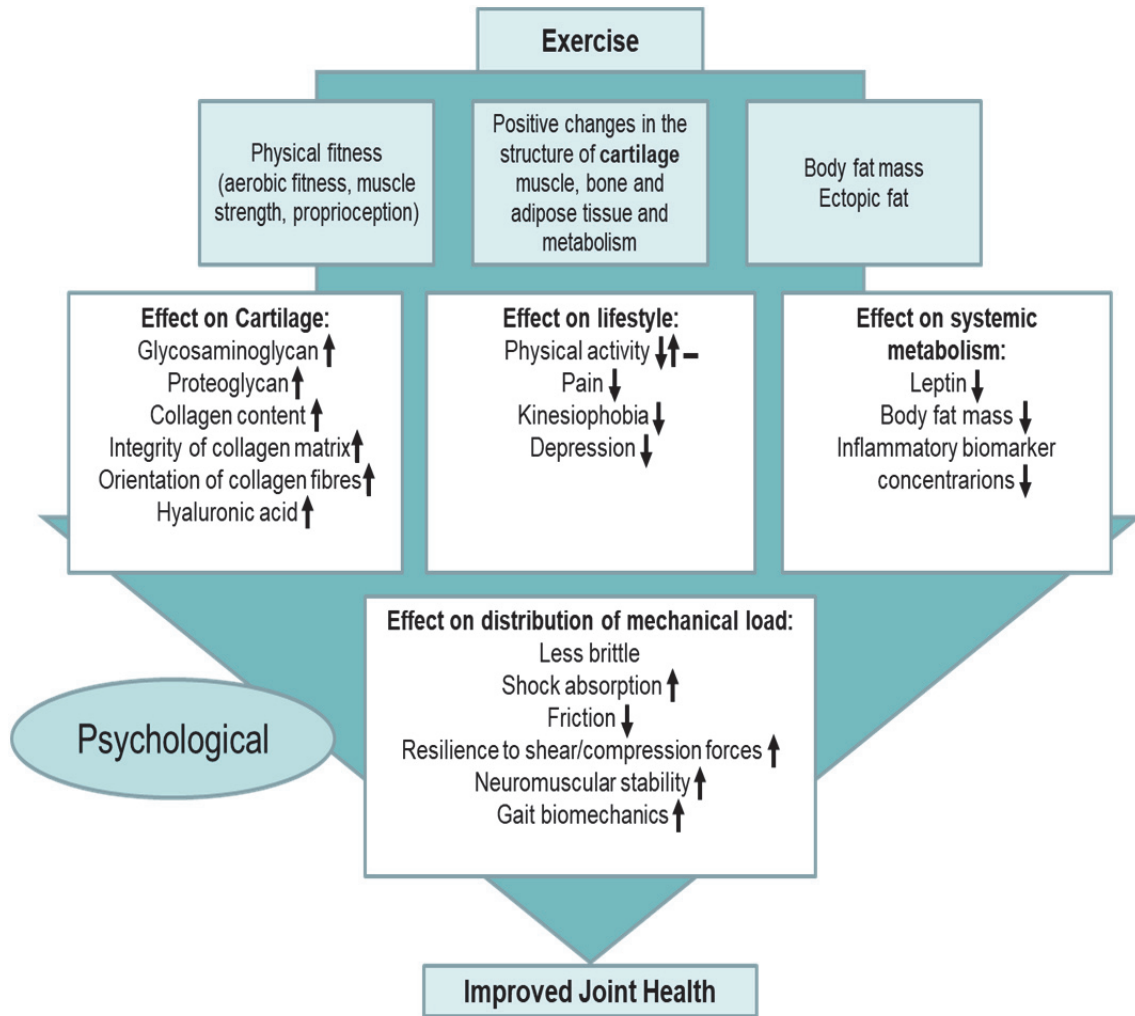


FIGURE 9 Loading to promote structural and neuromuscular adaptations for cartilage health according to Munukka & Waller 2018 (Unpublished).

3 PURPOSE OF THE STUDY

The primary objective of this thesis was to study the efficacy of progressive, high volume aquatic resistance training on the estimated biochemical composition of tibiofemoral cartilage (Study I) and the association between long-term leisure time physical activity and the estimated biochemical composition of tibiofemoral cartilage (Study III) in postmenopausal women with mild knee OA. Also, the short and long-term effects of aquatic resistance training on self-assessed function and quality of life was investigated (Study II). Moreover, the association between neuromuscular performance and lower limb bone strength was studied (Study IV).

The specific research questions were:

1. Does 4-month progressive, high volume aquatic resistance training enhance the estimated biochemical properties of tibiofemoral cartilage in postmenopausal women with mild knee OA? (Study I)
2. Does 4-month progressive, high volume aquatic resistance training improve self-assessed function and quality of life in postmenopausal women with mild knee OA and are the results maintained during a 12-month follow-up period? (Study II)
3. Is 12-month leisure time physical activity associated with changes in the estimated biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee OA? (Study III)
4. Does neuromuscular performance predict lower limb bone strength in different lower limb sites in postmenopausal women with mild knee OA? (Study IV)

4 RESEARCH METHODOLOGY

4.1 Study design and participants

This study utilizes data from a large randomized controlled trial (RCT) intervention project: AquaRehab (ISRCTN65346593) conducted at the Faculty of Sport and Health Sciences in University of Jyväskylä, Finland. Additional data from our previous RCT intervention project, LuRu (ISRCTN58314639), was utilized in a cross-sectional study (Study IV). AquaRehab project was conducted between January 2012 and July 2014, and LuRu project was conducted between March 2007 and April 2010.

A total of 87 participants from the Jyväskylä region in Central Finland were involved in the AquaRehab project (Studies I-III). Studies involved comprise data from a 4-month RCT (Study I) and a 12-month follow-up (Study II and Study III). Additionally, in the cross-sectional study (Study IV) utilizing data from LuRu project, the total amount of participants was 139.

Participants in both studies were volunteer postmenopausal women, aged 50-68 years, with mild knee OA (Kellgren Lawrence I/II and knee pain). An RCT titled "Intervention" assessed the effects of aquatic resistance training on cartilage, physical performance, self-reported functioning and symptoms of OA and quality of life (Study I). An RCT with follow-up titled "Intervention with 12-month follow-up" assessed if high volume aquatic resistance training improves self-assessed function and quality of life and the long-term maintenance of the possible effects (Study II). A 12-month follow-up study titled "Cartilage quality and LTPA" investigated the relationship between 12-month leisure time physical activity (LTPA) level and changes in estimated cartilage quality (Study III). A cross-sectional study titled "Neuromuscular performance and bone associations" used combined data set from LuRu and AquaRehab projects investigating if neuromuscular performance predicted lower limb bone strength (Study IV). All measurements in AquaRehab project were performed at baseline, after the 4-month intervention and after the 12-month

follow-up. The study designs, participants and main outcomes are summarized in Table 3.

4.2 Participant recruitment

In both RCT intervention projects, postmenopausal women from the Jyväskylä region in Central Finland were voluntarily recruited through advertisements in local newspapers. Preliminary eligibility was assessed using a structured telephone interview, followed by an evaluation of osteoarthritis severity in the tibiofemoral joint with radiographs and finally, through a medical and physiotherapy screening.

Inclusion criteria were: 1) a postmenopausal woman aged 50–68 years, 2) experiencing knee pain on most days, 3) participating in no more intensive exercise than brisk walking \leq twice a week, 4) radiographic changes in tibiofemoral joint K/L I or II, 5) no cancer or chemotherapy prior to the study, 6) no medical contraindications or other limitations to full participation in the exercise program.

Exclusion criteria were: 1) a T-score $< -2,5$ (indicating osteoporosis) (Kanis et al. 2008) measured from the femoral neck using dual-energy X-ray absorptiometry (DXA), 2) resting knee pain visual analogue scale (VAS) $>50/100$, 3) a body mass index (BMI) of $>34 \text{ kg/m}^2$ (due to confounding factors related to obesity in relation to intervention), 4) surgery of the knee due to trauma or knee instability, 5) meniscectomy within the last 12 months, 6) inflammatory joint disease, 7) intra-articular steroid injections in the knee during the previous 12 months, 8) contraindications to MRI and 9) allergies to contrast agents or renal insufficiency.

Inclusion criteria of the two research projects were otherwise similar except for age (AquaRehab age range: 60 - 68 years, LuRu: 50 - 66 years) and for BMI (AquaRehab: $\leq 34 \text{ kg/m}^2$, LuRu: $\leq 35 \text{ kg/m}^2$). Measurement protocols were similar in both studies, except for the pQCT measurement, in which affected knee side (i.e. higher knee K/L side) was measured in AquaRehab, whereas right tibia was always measured in LuRu.

TABLE 3 The summary of the study designs, participants and main outcomes.

Study	Data set	Study design	Participants	Age range, years	Main outcomes measures	Secondary outcomes measures
I	Aqua	RCT	87 postmenopausal women: Exercise group (n=43) Control group (n=44)	60-68	<ul style="list-style-type: none"> Tibiofemoral cartilage T2 relaxation time and dGEMRIC-index OA related symptoms Self-related functioning 	<ul style="list-style-type: none"> Cardiorespiratory fitness Isometric knee flexion and extension force
II	Aqua	RCT with 12-month follow-up	87 postmenopausal women: Exercise group (n=43) Control group (n=44)	60-68	<ul style="list-style-type: none"> OA related symptoms Quality of life 	<ul style="list-style-type: none"> N/A
III	Aqua	12-month follow-up	76 postmenopausal women: Lowest METH (n=25) Middle METH (n=25) Highest METH (n=26)	60-68	<ul style="list-style-type: none"> Tibiofemoral cartilage T2 relaxation time and dGEMRIC-index Physical activity data 	<ul style="list-style-type: none"> Cardiorespiratory fitness Isometric knee flexion and extension force OA related symptoms Self-reported functioning
IV	Aqua + LuRu	Cross-sectional	139 postmenopausal women	50-68	<ul style="list-style-type: none"> Femoral neck, Z, Tibial mid-shaft, SSI_{max,mid}, Distal tibia, BSI_d GRF, Power, concentric net impulse Isometric knee flexion and extension force Figure-of-8-running 	<ul style="list-style-type: none"> N/A

Aqua = AquaRehab study, LuRu: LuRu study, dGEMRIC = delayed gadolinium-enhanced MRI of cartilage, METH = metabolic equivalent task hours, Z = section modulus, SSI_{max,mid} = tibial mid-shaft density weighted maximal moment of inertia, BSI_d = distal tibia compressive bone strength index, GRF = ground reaction force

4.2.1 Intervention (Study I)

This study was a 4-month randomized controlled trial (Study I) assessing the effects of progressive, high volume aquatic resistance training on the biochemical composition of tibiofemoral cartilage, physical performance, self-reported functioning and symptoms of OA and quality of life. As an additional inclusion criterion for Study I, a complete T2 data set, i.e. the baseline and end measurement, needed to be imaged from each participant. The multistage recruitment process of the participants is presented in Figure 10.

After the baseline measurements and before the initiation of the exercise intervention, all participants were randomly assigned into the aquatic training group (n=43) and control group (n=44). All participants were randomly allocated with a three-digit identification number to blind researchers to intervention allocation and provision. A blinded statistician, only provided with ID and K/L grade, performed a computer-generated block randomization of size of 10, stratified according to K/L grade I or II. The MRIs were performed by external radiologists blinded to intervention allocation.

4.2.2 Intervention with 12-month follow-up (Study II)

This study used secondary data from RCT investigating the short- (4-month) and long-term (12-month) effects of aquatic resistance training on self-assessed function and quality of life in postmenopausal women with mild knee osteoarthritis (OA). This study implemented data from the AquaRehab -project (n=87 postmenopausal 60-68-year old women with mild tibiofemoral OA).

4.2.3 Cartilage quality and LTPA (Study III)

This study was a 12-month follow-up to the 4-month randomized controlled trial investigating the relationship between 12-month leisure time physical activity (LTPA) level and changes in the estimated biochemical composition of tibiofemoral cartilage. After original intervention, 76 participants completed the 12-month follow-up period. As an additional inclusion criterion for this study, each participant needed to have returned the physical activity diaries from the study period.

The participants were divided into tertiles based on their average monthly LTPA (MET_h) during the follow-up period, 1=lowest (n=25), 2=middle (n=25) and 3=highest (n=26).

4.2.4 Neuromuscular performance and bone associations (Study IV)

This study was a cross-sectional trial investigating whether neuromuscular performance predicts lower limb bone strength in different lower limb sites (femoral neck, tibial midshaft and distal tibia). This study used the combined baseline data from LuRu (n=52) and AquaRehab (n=87) -projects (n=139 postmenopausal 50-68-year-old women with mild tibiofemoral OA). An additional inclusion criterion for this study was that pQCT needed to be measured from the affected knee side (i.e. higher knee K/L side).

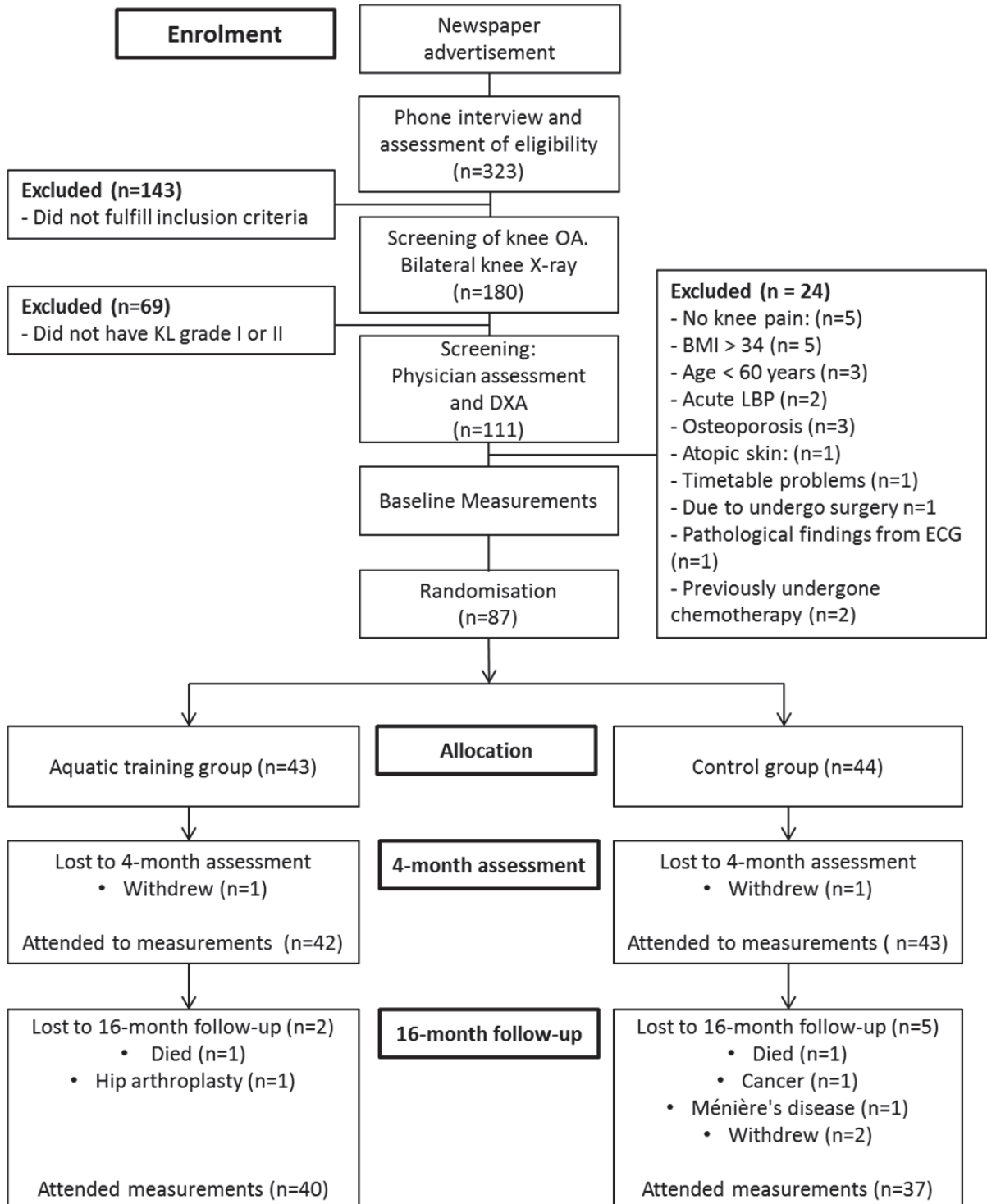


FIGURE 10 Flow chart of the intervention study.

4.3 Study approval and ethics

Both LuRu -research study protocol (Dnro1E/2008) and AquaRehab -research study protocol (Dnro 19U/2011) were approved by the Ethics Committee of the Central Finland Health Care District and conforms to the Declaration of Helsinki. Both studies were registered in the controlled trial database: LuRu (ISRCTN58314639) and AquaRehab: (ISRCTN65346593). All participants were informed about the measurement procedures and possible risk involved in each study and had medical insurance. A study physician was available for possible adverse effects during the whole intervention and follow-up periods. Written informed consent was obtained from all participants in both studies prior to enrolment. Access to collected data was restricted to the research study staff. A unique code was allocated to each participant to ensure confidentiality and anonymity. Only principal investigator had sole access to this data. Published results did not contain any personal data that could allow identification of individual participants. All electronic data was stored on University of Jyväskylä servers, with password protection. All paper-based data was securely stored in locked filing cabinets.

4.4 Measurements

4.4.1 Cartilage

The biochemical composition of the medial and lateral tibiofemoral cartilage was estimated using single-slice transverse relaxation time (T2) mapping and delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC index) (Studies II and IV). These methods provide information on the response of tibiofemoral cartilage to physiological loading (Roos & Dahlberg 2005, Mosher, Liu & Torok 2010). T2 is a surrogate for the properties of the collagen network with lower values corresponding to better integrity and orientation of the collagen fibres and the hydration of the articular cartilage (Lammentausta et al. 2006, Subburaj et al. 2012). dGEMRIC index measures estimated GAG content of the knee articular cartilage with higher values corresponding to higher estimated GAG concentration (Bashir et al. 1999, Binks et al. 2013). dGEMRIC index, i.e. spin lattice relaxation time (T1) was performed in the presence of gadolinium diethylene triamino pentaacetic acid (Gd [DTPA]²⁻). Images were taken 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 imaged knee in slight flexion, stabilized in a leg holder and a custom made inflatable cushion. The cushion was specifically designed to stabilize the patella without causing any compression of the patellofemoral joint.

Single sagittal slice images from the centre of the medial and lateral femoral condyles were taken from the knee with the highest K/L grade (affected knee). In the cases where both knees had identical K/L score the right knee was imaged. The imaging session lasted three hours and included a standard clinical MRI series and T2 relaxation time followed by the dGEMRIC series. T2 mapping was performed using a sagittal multi-slice multi-echo fast spin echo sequence (field of view [FOV] 14cm, acquisition matrix 256 x 256, repetition time [TR] 2090 ms, eight echo times [TE] between 13 and 104 ms, echo train length [ETL] 8, slice thickness 3 mm). The slices were positioned perpendicular to a line tangential to the posterior femoral condyles in the axial scout view. Two slices, each covering the central region of the medial and lateral condyles, were analyzed.

For the dGEMRIC series, immediately after the clinical and T2 imaging, an intravenous injection of 0.4mL/kg (double dose) of Gd-DTPA²⁻ (Magnevist, Schering, Berlin) was administered. The amount of contrast agent administered was corrected for body weight at each measurement point. This was appropriate because of the expected changes in body composition as a result of the intensive exercise intervention. In order to enhance the delivery of the contrast agent into the knee cartilage, following administration of Gd-DTPA²⁻, the participants were instructed to perform five minutes of knee flexion-extension exercises in a sitting position without resistance, five minutes of walking on a flat surface and ten gentle deep squats. Exactly ninety minutes after the injection, dGEMRIC mapping in the presence of Gd-DTPA²⁻ was performed in the sagittal plane using a single slice inversion recovery fast-spin echo sequence (FOV = 14 cm, matrix 256 x 256, TR = 1800 ms, TE 13 ms, six inversion times [TI] between 50 and 1600 ms, slice thickness 3 mm). The slice positioning was copied from the T2 relaxation time mapping sequence, and the number of the slice in the correct orientation is reduced to one. The remaining slice was then positioned at the centre of the medial and lateral condyles as viewed on the axial scout image. The participants were positioned in an identical position with the first MRI imaging. For quality assurance purposes, a set of phantom samples containing certain concentrations of agarose and nickel nitrate to modulate their dGEMRIC and T2 relaxation times were imaged following the study protocol prior to the baseline and follow-up measurement sessions, and no evidence of scanner drift was observed during the intervention.

Cartilage regions of interest (ROIs) from the single sagittal slices at the centre of the medial and lateral tibial and femoral condyles were manually segmented using a semi-automated in-house MATLAB application with built-in motion correction for dGEMRIC (Mathworks, Inc. Natick, MA, USA). Entire visible cartilage of the femur and tibia was manually segmented and divided into three ROIs; anterior, central and posterior, and further, automatically divided for the superficial and deep halves of the cartilage thickness (Figure 11). dGEMRIC indices were corrected for BMI (Tiderius et al. 2006). Precision, scan-rescan, (CV_{RMS}) of dGEMRIC in asymptomatic subjects is 7% for full-thickness ROIs and 5% for bulk cartilage (Multanen et al. 2009). In our laboratory, the in-

ter-observer error (CV_{RMS}) for T2 full-thickness ROIs was 1.3% to 3.3% and 2.8% to 4.0% for the dGEMRIC index.

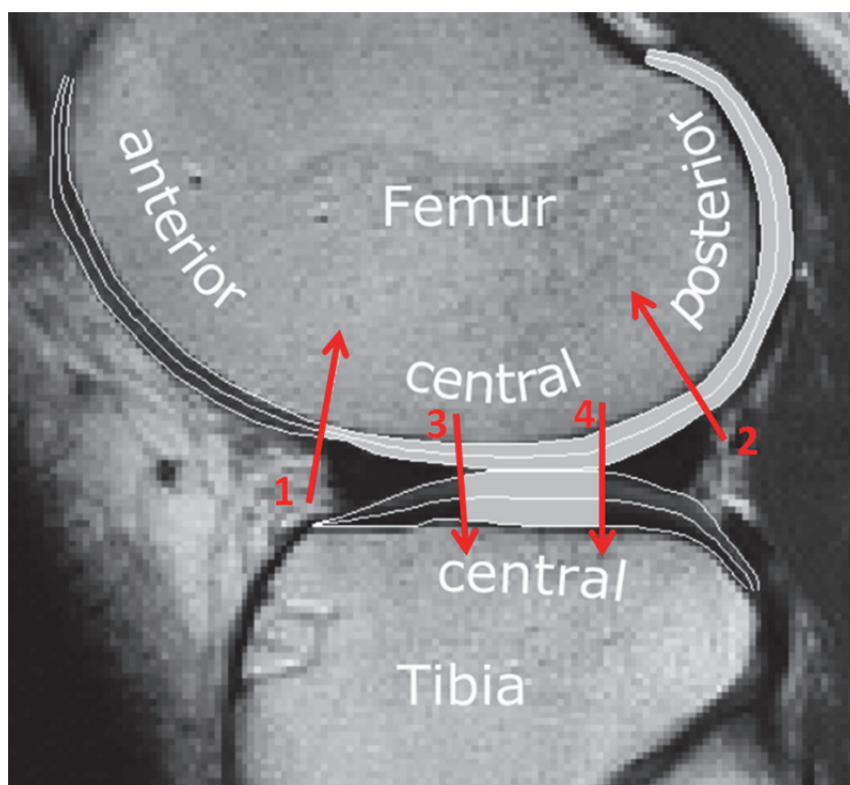


FIGURE 11 Illustration of the region of interests (ROIs) in the full-thickness femoral and tibial cartilage. Midlines split both femoral and tibial cartilage into superficial and deep sections. ROIs were segmented according to the landmarks as follows for central femoral cartilage: from the anterior end of anterior meniscus (arrow 1) to the posterior end of the posterior meniscus (arrow 2) and for central tibial cartilage: from the posterior end of anterior meniscus (arrow 3) to the anterior end of the posterior meniscus (arrow 4).

4.4.2 Cardiorespiratory fitness

Cardiorespiratory fitness (VO_2 peak, ml/kg/min) was assessed using the UKK 2 km walking test (UKK Institute, Tampere, Finland) which required the participant to walk 2km as fast as possible with a target of 80% maximal heart rate (Laukkanen et al. 1993). VO_2 peak was estimated using the participant's BMI, age, walking time and heart rate at the end of the test. The heart rate was monitored using heart rate monitors (Polar F6, Electro Ltd, Kempele, Finland). A 2km walking test is valid (correlation coefficient between the measured and predicted VO_2 peak: 0.69 - 0.77) (Laukkanen et al. 1992) and feasible for assessing VO_2 peak (Laukkanen et al. 1992) and sensitive to changes (Kukkonen-Harjula et al. 1998).

4.4.3 Daily physical activity

Daily physical activity of each participant was registered using a leisure time physical activity diary for the whole study period (16mo). Out of the diary, the metabolic equivalent task (MET-hours) per week was calculated (Ainsworth et al. 2011) (Studies II-III). On week 13 of the intervention period the daily physical activity (excluding intervention) was measured for three consecutive days including one weekend day using an accelerometer (Hookie AM 20, Traxmeet Finland) (Study II). Mean amplitude deviation (MAD) of the resultant acceleration signal for each 5-sec epoch were calculated and categorized according to Vähä-Ypyä et al. 2015 (Study II).

4.4.4 Self-reported symptoms

Self-assessed impact of OA on pain, other symptoms, activities of daily living, sports and recreation and knee-related quality of life were assessed using the validated Finnish (Koli et al. 2011) Likert version of the knee injury and osteoarthritis outcome score (KOOS) questionnaire (Roos et al. 1998) (Studies II-III). Scores for each domain range between 0 and 100, with a score of 0 indicating extreme and 100 no knee problems. In studies I and IV, self-reported pain, stiffness and physical functional difficulty were assessed by Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire with a range from 0 to 100 mm in the visual analogue scale (VAS) (Bellamy et al. 1988).

4.4.5 Self-reported quality of life

Self-reported physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health were assessed by using the Short Form Health Survey (SF-36). Scores for each domain range between 0 and 100, with a score of 0 indicating the worst overall health status and 100 the best health status (Angst, Aeschlimann & Stucki 2001). Two distinct summary components, mental and physical, were aggregated from the eight domains by using US reference population (1990) for standardization and for factor score coefficients. Furthermore, the mental and physical components were standardized using a mean of fifty and standard deviation of 10 (Ware & Kosinski 2001). Version 1.0 of the SF-36 was used in this study.

4.4.6 Lower limb bone and body composition

Dual-energy X-ray absorptiometry (DXA)

DXA (Lunar Prodigy; GE Lunar Healthcare, Madison, WI, USA) was used to assess the rigidity of femoral necks and whole body composition (Study I). Proximal femur was scanned with DXA at the narrowest neck section. Femoral neck section modulus (Z , [mm³], an index of bending strength) was calculated with advanced hip structural analysis (AHA) as per manufacturer's software (Beck 2007). The femoral neck section modulus (Z) is equal to the cross-sectional moment of inertia (CSMI) divided by the distance from the center of mass to the superior neck margin (y). Coefficient of variation (CV) of femoral neck section modulus (Z) has been assessed to be 5.1% in our laboratory. Total body fat mass and lean mass were analyzed using enCORE software (enCORE 2011, version 13.60.033) for those subjects in AquaRehab study only (n=87). *In vivo* precision of these measurements has been reported to be CV of 1.3-2.2% (Uusi-Rasi et al. 2010).

Peripheral quantitative computed tomography (pQCT)

pQCT (XCT 2000, Stratec Medizintechnik GmbH, Pforzheim, Germany) was used to assess the rigidity of the distal and mid-shaft of the tibia from the affected side leg at 5% and 55% of the length of the tibia from the distal end to the mid-shaft of the tibia (Study I). A 30 mm planar scout view of the distal tibia was used to define the distal end of tibia. Distal tibia compressive (BSI_d , g²/cm⁴) and tibial mid-shaft bending ($SSI_{max_{mid}}$, mm³) strength indices were calculated from the data obtained using pQCT. The BSI_d was calculated as:

$$BSI_d = TtD_d^2 * TtAr_d \quad (1)$$

where TtD_d^2 is the apparent bone density of the total bone cross-section and $TtAr_d$ the total cross-sectional area of the distal tibia (Equation 1). The $SSI_{max_{mid}}$ was calculated as:

$$SSI_{max_{mid}} = \sum_{i=1}^n \frac{y_i^2 * D_i * ar}{1200 * y_{max_{mid}}} \quad (2)$$

where i = index of voxel, D_i = Density of the i :th voxel (in mg/cm³), ar = area of voxel, y_i = distance of the i :th voxel from the bending axis corresponding to the maximal cross-sectional moment of inertia and $y_{max_{mid}}$ = the distance of the most anterior point from the bending axis corresponding to the maximal cross-sectional moment of inertia (Equation 2) (Rantalainen et al. 2010).

pQCT bone strength indices predict robustly bone failure in compression at the distal tibia and bending strength at the tibial diaphysis (Kontulainen et al. 2008). CV for the reported pQCT variables has been measured to range from 0.4

to 1.6% in our laboratory (Rantalainen et al. 2008). DXA and pQCT were measured from the higher K/L grade knee side.

4.4.7 Neuromuscular performance

Counter movement jump test (CMJ)

Dynamic maximal muscle power of lower limbs was examined by measuring ground reaction forces in newtons (GRFs, N), peak instantaneous power production during the takeoff phase in watts (W) and concentric net impulse in newton seconds (Ns) with a custom made (University of Jyväskylä, Jyväskylä, Finland) force platform during counter movement jump test (Study I). Participants were asked to perform a counter movement jump with hands on hips and were instructed to jump as high as possible with the preferred counter movement depth and velocity. The weight of the subject was subtracted from the recorded vertical ground reaction force and then divided by the body mass of the subject to produce vertical acceleration (Rantalainen et al. 2010). Results from the vertical ground reaction force were analyzed using a custom made Matlab script. Maximal power traits were extracted following the methodology from our previous study (Rantalainen et al. 2010). Variation coefficients of 2.5% for jump height (Torvinen et al. 2002) and 3.6% for power (Rittweger et al. 2004) have been reported in the counter movement jump.

Maximal isometric force

Knee extension and flexion force of both legs was measured using an adjustable computer-linked dynamometer chair (Good strength, Metitur Ltd, Jyväskylä, Finland) and recorded in newtons (N) (Studies I-III). The leg that was measured first was chosen randomly to ensure that in later measurement points the known tendency to perform better randomly hits the affected or non-affected knee side. As preparation for the measurements, the measured knee was set at an angle of 60° from the full extension with the ankle strapped with a belt above the malleolus to a strain gauge. One practice trial and four maximal efforts were performed, separated by a 30-second rest period, until no further improvement was observed. The best performance was chosen for the analysis. The precision of the tests in our laboratory is 6.3% for the knee extension force and 8.5% for the knee flexion force (Sipilä et al. 1996).

Figure-of-8 running test

Standardized Figure-of-8 running test was used to measure dynamic balance and agility (Study I). Test started from a standing start and consisted of running two laps as fast as possible in a figure of eight around two cones placed ten meters apart. Photocells were used to measure the time in seconds taken to complete the task. After a practice trial, the best of three attempts with the shortest time was chosen for analysis. The test has been shown to be sensitive (73.5%)

and specific (86.1%) for measuring agility and to be effective at detecting decreased motor performance (area under curve 0.86) (Rinne et al. 2006).

4.4.8 Background characteristics of the study participants

Severity of radiographic knee OA

Study participants from both AquaRehab and LuRu research projects underwent x-ray imaging (postero-anterior view of the tibiofemoral joint in a semi-flexed weight bearing position) of both knees. The severity of the knee osteoarthritis was evaluated by experienced musculoskeletal radiologists, assessing the degree of OA in the tibiofemoral joints using the K/L grading (Kellgren & Lawrence 1957). Participants with mild knee OA, i.e. radiographic changes in tibiofemoral joint grades I (doubtful narrowing of joint space, possible osteophytes) or II (definite osteophytes and joint space narrowing), were included in the studies.

General Health

Body mass and body height were measured using standard procedures. Body mass index was calculated as mass (kg) divided by height (m) squared. Also, a researcher-designed questionnaire was used to record physical activity levels, general health, medical conditions, current medications, menopausal status and hormone therapy. Leisure time physical activity levels, i.e. activity type (e.g. walking or golf), duration and intensity, prior to the study inclusion were converted into MET -hours per week (Ainsworth et al. 2011). Additionally, physical or medical limitations to the full participation in the measurements or intervention were assessed by structured medical and physiotherapy screening by an attending physician and physiotherapist respectively. The severity of restricted joint range of movement (ROM), excessive laxity of knee joint, possible physical disabilities and abnormalities found from resting echocardiogram were assessed.

4.5 Progressive aquatic resistance training

4.5.1 Aquatic training protocol

The intervention protocol implemented in this study was adapted from a previously used protocol shown to be effective in healthy women (Pöyhönen et al. 2002) and people with post-knee arthroplasty (Valtonen et al. 2010). Aquatic steps were used to ensure that all subjects were able to complete the standing exercises at a depth level approximately to their xiphoid bone ± 5 cm ensuring weight bearing of 25-50% of own body weight on the supporting leg. The progression of the training was achieved by using resistance boots of different sur-

face area to increase resistance (Pöyhönen et al. 2002): small fins with a frontal area of 0.0181m² (THERABAND PRODUCTS, The Hygienic Corporation, Akron, OH 44310 USA) and large boots with a frontal area of 0.075m² (Hydro-Tone hydro-boots, Hydro-Tone Fitness Systems, Inc. Orange, CA 92865-2760, USA).

The participants in the intervention group received one hour of supervised lower limb aquatic resistance training three times a week for 16 weeks, for a total of 48 training sessions. Each one-hour-long session consisted of:

Warm up

A 10-15 minute warm up that consisted of ten different movements to increase active ROM of all joints and enhance neuromuscular activation. Each movement was completed for 1 min (30 s per leg when alternating leg) with 15 s rest period. The order of the movements was altered for each session to maximise neuromuscular stimulation and prevent staleness as well as to maintain participants' interest.

Progressive aquatic resistance training

A 30-35 min intensive aquatic resistance training program consisted of five exercises (Figure 12). The resistance of the exercises was progressed with three different levels: barefoot, small fins and large resistance boots (Pöyhönen et al. 2002), and the training leg performed all movements without contact with the pool walls or bottom, i.e. non-weight-bearing. The intervention was completed in small groups of 6-8 subjects in a pool heated to 30-32 degrees with two instructors: one ensuring intensity and the other ROM. The instructors also recorded the attendance of each participant. Intensity of the training sessions was set at "as hard and fast as possible" through full ROM to ensure maximal muscle contraction. Pöyhönen et al. (2001) discovered that during maximal knee flexion and extension exercises in water with large resistance boots, the drag forces produced were 80-85% (145 ± 30 N) of maximal isokinetic movements. Full ROM was strictly controlled in order to ensure optimal movement of synovial fluid and exposure of the whole cartilage to the low compressive and shear forces created by muscle contraction and movement. Training intensity during each session was evaluated by collecting mean and maximum heart rate values using heartbeat monitors (Polar Electro Ltd, Kempele, Finland) and a rate of perceived exertion (RPE) using the Borg 6-20 scale (Borg 1982). Target training zone was 60-80% of maximum heart rate according to the Karvonen formula, e.g. 60% training limit $(220 - \text{age}) \times 0.6$ and 80% training limit $(220 - \text{age}) \times 0.8$. The number of repetitions achieved per movement and blood lactate was measured on three different occasions. Daily progression of the aquatic resistance program is presented in Table 4.

Cool down

A 10-minute cool down consisted of 3-5 min of walking and supported cycling against pool wall and stretching, with 30 s of stretching for each side.

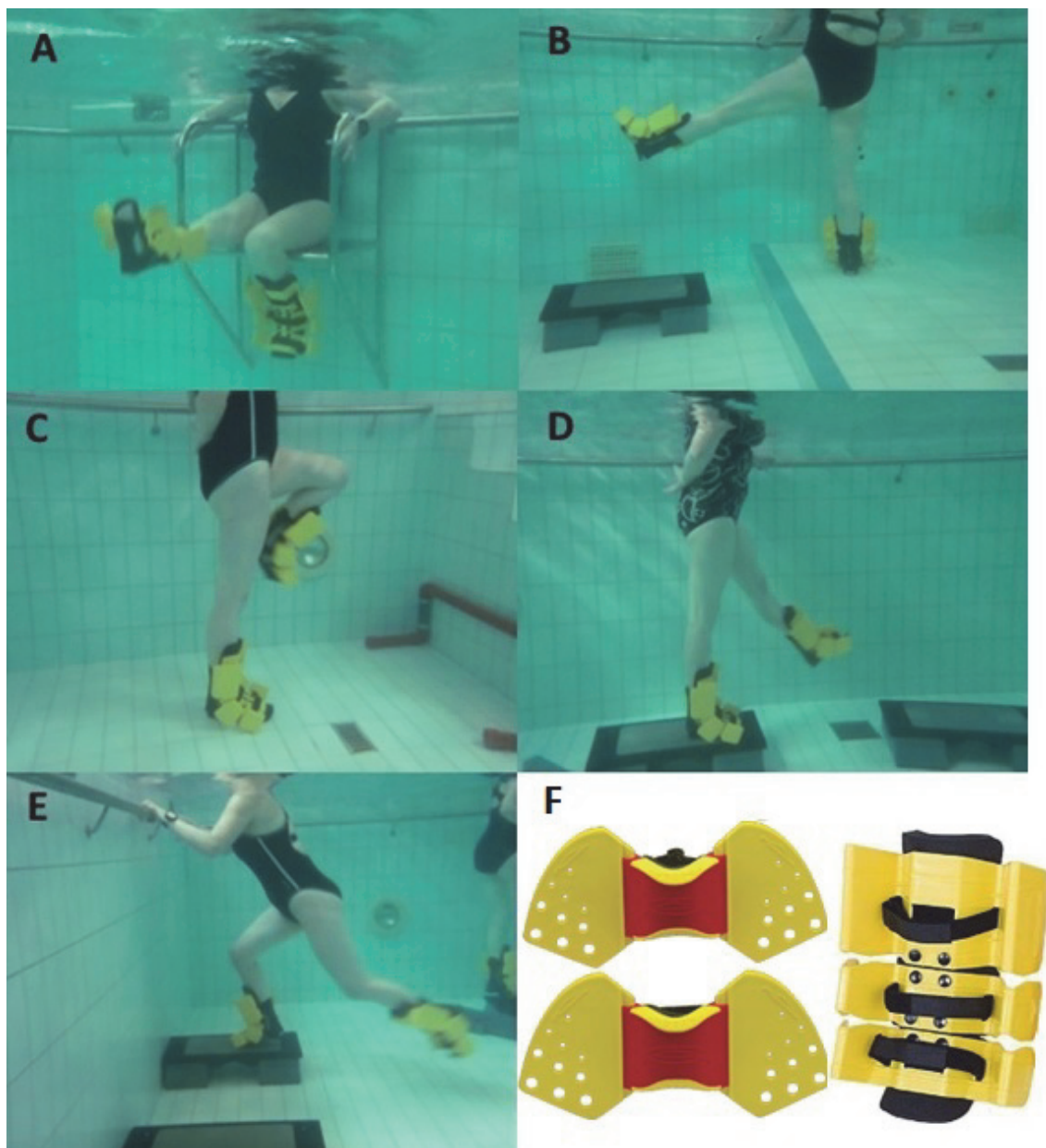


FIGURE 12 Illustrations of the exercises used in the 30 minute intensive aquatic resistance intervention. A: Knee flexion/extension when sitting, B: Hip adduction/abduction, C: Knee flexion/extension when standing, D: Hip flexion/extension with knee straight, E: Kickback, F: The fins and boots used to assure the progression of the training.

TABLE 4 Daily progressions of the aquatic resistance training program.

Month	Week	Session No.	Resistance	Intensity RPE (6-20)	Sets x duration (s) per leg	Recovery (s)	
1	1	1	Barefoot	12 - 14	2 x 30	30	
		2			2 x 45	30	
		3			3 x 45	30	
	2	2	4	Barefoot	12 - 14	3 x 45	30
			5			3 x 30	45
			6			3 x 45	30
	3	3	7	Small fins	15 - 16	3 x 45	30
			8		16 - 17	3 x 30	45
			9		15 - 16	3 x 45	30
	4	4	10	Small fins	16 - 17	3 x 30	45
			11		15 - 16	3 x 45	30
			12		16 - 17	3 x 30	45
2	5	13	Small fins	15 - 16	3 x 45	30	
		14		15 - 16	3 x 45	30	
		15		15 - 16	3 x 45	30	
	6	6	16	Small fins	16 - 17	3 x 45	30
			17	Large boots	16 - 17	3 x 45	30
			18	Small fins	15 - 16	3 x 45	30
	7	7	19	Large boots	16 - 17	3 x 45	30
			20	Small fins	15 - 16	3 x 45	30
			21	Large boots	16 - 17	3 x 45	30
	8	8	22	Large boots	16 - 17	3 x 45	30
			23	Small fins	15 - 16	3 x 45	30
			24	Large boots	16 - 17	3 x 45	30
3	9	25	Large boots	16 - 18	3 x 45	30	
		26			3 x 30	45	
		27			3 x 45	30	
	10	10	28	Large boots	16 - 18	3 x 30	45
			29			3 x 45	30
			30			3 x 30	45
	11	11	31	Large boots	16 - 18	3 x 45	30
			32			3 x 45	30
			33			3 x 45	30
	12	12	34	Barefoot	16 - 18	3 x 45	30
			35	Small fins		3 x 45	30
			36	Large boots		3 x 45	30
4	13	37	Large boots	16 - 18	3 x 45	30	
		38			3 x 30	45	
		39			3 x 45	30	
	14	14	40	Large boots	16 - 18	3 x 45	30
			41			3 x 30	45
			42			3 x 45	30
	15	15	43	Large boots	16 - 18	3 x 45	30
			44			3 x 30	45
			45			3 x 45	30
	16	16	46	Large boots	16 - 18	3 x 45	30
			47	Large boots		3 x 45	30
			48	Barefoot		15 - 16	3 x 30

4.5.2 Adverse effects

Adverse effects or health problems related to the exercise intervention or testing protocol were recorded and reported. After each training session (Study I) and individual measurement, self-reported knee pain was assessed using a visual analogue scale (VAS) along with any other physical symptom such as pain anywhere else, general fatigue and stiffness.

4.5.3 Control group

The control group were encouraged to continue their usual leisure time physical activities. They were offered the possibility of participating in two sessions consisting of one hour of light stretching and relaxation during the 4-month intervention period.

4.6 Statistical methods

The data in descriptive statistics are presented as means with standard deviations (SD) or as counts with percentages. Kolmogorov-Smirnov and Shapiro-Wilk W tests were used to test normality for continuous variables. Statistical comparisons were made by using t-test or analysis of variance (ANOVA) (Study I). The bootstrap method was used when the theoretical distribution of the test statistics was unknown or in the case of violation of the assumptions (e.g. non-normality).

Analysis of covariance (ANCOVA, Studies I and II)

Intervention and 12-month follow-up effect between aquatic resistance training and control group in all outcomes were analysed using the bootstrap type analysis of covariance (ANCOVA) with 4-month and 12-month measurements as depended variables. Confidence intervals were obtained by bias-corrected bootstrapping (5,000 replications) due to violation of distributions assumptions. T2 relaxation time was adjusted for the baseline value, height and weight, and dGEMRIC index was adjusted for the baseline value only. Secondary outcomes, i.e. physical performance and self-reported symptoms, were adjusted for the baseline value. There were multiple endpoints in Studies I and II, therefore all p-values and confidence intervals are quoted, rather than introducing the problems and potential errors associated with formal adjustments for potential multiplicity issues. Effect sizes (d) were calculated by using the method of Cohen (Faraone 2008), where an effect size of 0.20 is considered small, 0.50 moderate, and 0.80 large. Confidence intervals for the effect sizes were obtained by bias-corrected bootstrapping (5,000 replications).

Generalized linear models (Study III)

Statistical significance for the hypothesis of linearity between physical activity tertiles (lowest, middle and highest) with cartilage and physical performance traits were evaluated by using analysis of variance (ANOVA) and analysis of covariance (ANCOVA). T2 was adjusted for the baseline value, height and weight. dGEMRIC index, which was already adjusted for BMI, and secondary outcomes were adjusted for the baseline value only. The normality of the variables was tested by using the Shapiro-Wilk W test. Since two participants (2.6%) had missing LTPA diary data, the last observation carried forward method was used.

Standardized regression coefficients Beta (β) (Study IV)

Linear regression analyses were used to identify the appropriate predictors of the bone strength indices using unadjusted and adjusted (height, weight and age) standardized regression coefficients Beta (β). The Beta value is a measure of how strongly each predictor variable influences the criterion (dependent) variable. The beta is measured in units of standard deviation. Cohen's standard for Beta values above 0.10, 0.30 and 0.50 represent small, moderate and large relationships, respectively. Hochberg's procedure was used to correct type I error. Correlation coefficients between bone strength indices and body composition were calculated by using the Pearson method and Sidak adjusted probabilities.

Statistical software

Stata versions 13.1 (Studies I and II) and 14.1 (Studies III and IV) of the StataCorp LP (College Station, TX, USA) statistical package were used for the analyses the studies.

5 RESULTS

5.1 Characteristics of the study participants

The baseline demographic and clinical characteristics of the study participants are summarized in Table 5. In the intervention studies (Studies I and II), the demographic and clinical characteristics of both groups were similar at baseline.

In the demographic and clinical characteristics of study participants according to the LTPA (MET_h) (Study III) at baseline there was a linear relationship between body mass ($p < 0.001$), BMI ($p < 0.001$), cardiorespiratory fitness (VO_{2peak} , $p < 0.001$), muscle force (knee extension, $p < 0.001$, knee flexion, $p = 0.011$) and LTPA level. Most common LTPAs during the 12-month follow-up period were walking (including Nordic walking) (mean: 1h 5min/week, 1h 38min/week and 3h/week in the tertiles, respectively) and LTPA described as "other" (e.g. gardening and cleaning) (mean: 55min/week, 1h 13min/week and 1h 28min/week in the tertiles respectively).

TABLE 5 Baseline demographic and clinical characteristics of the participants, means (SD) or n (%).

	<u>Studies I and II</u>		<u>Study III</u>		<u>Study IV</u>	
	Exercise group (n=43)	Control group (n=44)	Lowest METH (n=25)	Middle METH (n=25)	Highest METH (n=26)	Combined data (n=139)
Age (years)	64 (2)	64 (2)	64 (2)	64 (3)	65 (2)	62 (4)
Height (cm)	162 (5)	162 (5)	162 (5)	161 (5)	163 (4)	162 (5)
Body mass (kg)	69.6 (10.3)	71.0 (11.3)	76.4 (10.8)	69.1 (10.8)	65.3 (9.1)	71 (11)
Body mass index (kg/m ²)	26.6 (3.8)	27.1 (3.5)	28.9 (3.4)	26.6 (3.8)	24.5 (3.0)	27 (4)
Time from menopause (years)	14 (6)	14 (6)				12 (6)
Pain killers for knee pain, n (%) of users	11 (25.6)	9 (20.5)				46 (33)
Glucosamine use occasionally, n (%)	12 (28)	8 (18)				36 (26)
Kellgren Lawrence grade, n (%)						
Grade 1	23 (53.5)	24 (54.5)				
Grade 2	20 (46.5)	20 (45.5)				
Knee pain (VAS, mm) ^a						
• Affected leg	28 (25)	24 (19)				
• Non-affected leg	24 (19)	23 (18)				
Habitual physical activity (METH/week)	29 (31)	36 (33)				22 (20)
KOOS (0-100)						
Pain	80 (10)	82 (12)	83 (11)	85 (11)	85 (11)	
Other symptoms	74 (13)	75 (14)	80 (12)	80 (13)	81 (13)	
ADL	84 (10)	85 (11)	86 (12)	88 (14)	88 (10)	
Sport	63 (20)	65 (22)	67 (24)	69 (30)	73 (17)	
QOL	65 (17)	71 (20)	72 (20)	76 (22)	76 (18)	

TABLE 2 Continues

	Exercise group (n=43)	Control group (n=44)	Lowest METH (n=25)	Middle METH (n=25)	Highest METH (n=26)	AquaRehab and LuRu (n=139)
WOMAC (VAS 0-100 mm)						
Pain	13 (12)	13 (13)				11 (11)
Stiffness	18 (18)	22 (22)				16 (18)
Physical function	9 (9)	10 (12)				8 (9)
SF-36						
Physical functioning	79 (13)	81 (13)				
Role-Physical	83 (26)	85 (31)				
Bodily Pain	69 (17)	73 (15)				
General Health	71 (16)	75 (13)				
Vitality	71 (17)	76 (17)				
Social Functioning	90 (18)	92 (15)				
Role-Emotional	84 (29)	92 (22)				
Mental Health	81 (14)	83 (17)				
Summary Physical Health Scale	47 (6)	48 (7)				
Summary Mental Health Scale	55 (9)	56 (10)				
Muscle force (N)						
Extension	335 (64)	343 (70)	336 (71)	377 (53)	362 (70)	365 (82)
Flexion	164 (52)	165 (40)	178 (38)	190 (34)	185 (51)	174 (50)
Cardiorespiratory fitness, (ml/kg/min)						
Estimated VO _{2 peak}	24.6 (5.6)	24.9 (4.9)	24.6 (3.9)	26.8 (5.9)	29.5 (4.1)	

METH = metabolic equivalent task hour, KOOS = Knee Injury and Osteoarthritis Outcome Score, ADL= activities of daily living, Sport = sports and recreation, QOL = knee related quality of life, WOMAC = Western Ontario and McMaster University Osteoarthritis Index.
^a Estimated knee pain during last week. Range, 0-100 mm.

5.2 Effects of progressive aquatic resistance training in postmenopausal women with mild tibiofemoral OA

In total 87 participants met the inclusion criteria and were randomized into the aquatic training group (n=43) and control group (n=44). During the 4-month intervention period, no between-group differences were seen in daily LTPA (METh) once the intervention activity was removed or in physical activity as measured with accelerometers using mean amplitude deviations (MADs), excluding the intervention.

5.2.1 Feasibility of the training program

Drop-out rate during the 4-month intervention period for each group was 2.3% (one intervention and one control). Training compliance was 88% and mean (SD) training frequency was 2.6 (0.5) per week (drop outs included). The average self-assessed intensity of training sessions was RPE 15 (range, 12-17) and average (SD) maximum heart rate was 144 (12) beats per minute. The mean (SD) number of repetitions completed per session with the affected leg was 481 (67), 416 (68) and 387 (58) for barefoot, small fins and large boots respectively. 70.5% of the repetitions involved full knee active extension and flexion, which was mean 134.4 (SD, 5.6) degrees (affected knee) as measured during the baseline assessment.

5.2.2 Harms

Two trainees consulted the attending physician (bilateral knee pain and dyspnoea) as a result of the aquatic training. One subject from the control group required a medical consultation for knee pain after the baseline physical performance measures. All three subjects continued their participation in the study and attended end measurements.

5.2.3 Feasibility of the cartilage analysis

To ensure accuracy, each MRI image was inspected for quality. One participant was excluded from the study due to corrupted data as a result of excessive movement artefact in T2 images. One complete baseline dGEMRIC index data set was missing due to lost images (at time of imaging). Additionally, from the dGEMRIC index 11 medial compartments had movement artefact, while in the lateral compartment, 14 had artery-flow pulsating artefact, one had movement artefact and there was one inaccurate location of the slice compared to the baseline image. In total 72 and 68 complete dGEMRIC data sets for medial and lateral femoral condyles, respectively, were available for quantitative analysis.

5.2.4 Training effects on cartilage quality

After four months of progressive aquatic resistance training, a significant decrease was observed in both T2, mean difference -1.2ms (95%CI: -2.2 to -0.2 , $p=0.021$) and dGEMRIC index -23ms (-43 to -3 , $p=0.022$) in the training group compared to controls in the full thickness posterior ROI of the medial femoral cartilage (Table 6). Further, significant decreases in the training group compared to controls were only seen in the deep posterior and not superficial ROI of the medial femoral cartilage, -1.6ms (-3.0 to -0.3 , $p=0.016$), and -26ms (-50 to -3 , $p=0.030$), for T2 and dGEMRIC index respectively (Figure 13).

In the additional analysis for this thesis we found that these between group differences were lost at the 12-month follow-up, -0.7ms (-1.9 to 0.4 , $p=0.198$) and -11ms (-41.5 to 19.3 , $p=0.468$) for full-thickness medial T2 and dGEMRIC index respectively.

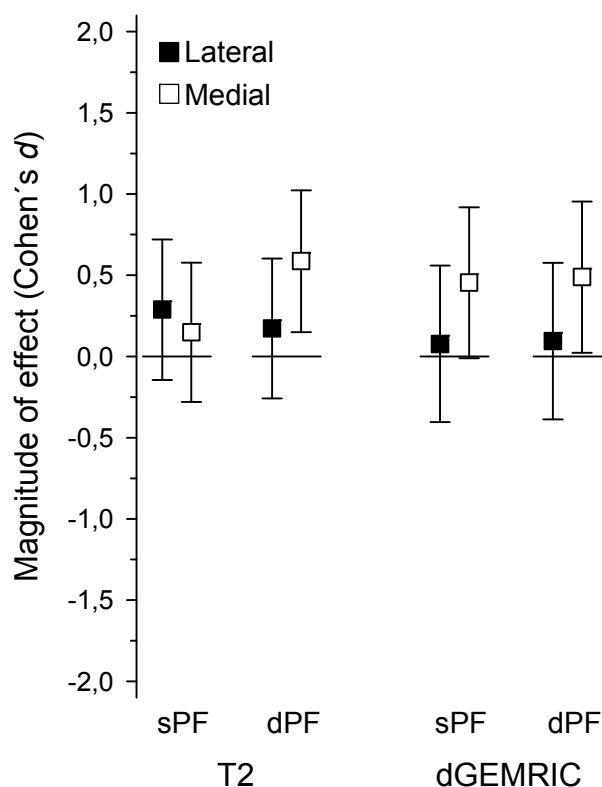


FIGURE 13 Magnitude of effect (Cohen's d and 95% CI) at superficial and deep layers of T2 and dGEMRIC cartilage ROIs from medial and lateral condyles. T2 = transverse relaxation time; dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage; sPF = superficial posterior femur; dPF = deep posterior femur.

TABLE 6 Effects of aquatic training on T2 relaxation time and dGEMRIC index in full-thickness ROIs.

	Baseline, mean (SD)		Change to month 4, mean (95% CI)		Effect Size (95% CI)		P-value	
	Training (n=42)	Controls (n=42)	Training (n=42)	Controls (n=42)	Crude	Adjusted	Crude	Adjusted
Femur, T2 (ms)								
Lateral condyle								
Central	52.6 (4.9)	53.4 (4.1)	-0.18 (-1.05 to 0.59)	-0.03 (-0.95 to 0.91)	0.05 (-0.38 to 0.48)	0.81	0.81	0.58 ^a
Posterior	49.6 (4.6)	48.8 (3.6)	-0.23 (-1.26 to 0.97)	0.74 (0.01 to 1.40)	0.31 (-0.12 to 0.74)	0.15	0.15	0.30 ^a
Medial condyle								
Central	52.8 (4.5)	52.0 (4.4)	-0.20 (-1.17 to 0.83)	0.48 (-0.71 to 1.68)	0.18 (-0.25 to 0.61)	0.40	0.40	0.47 ^a
Posterior	52.0 (4.7)	51.9 (4.5)	-1.16 (-1.85 to -0.50)	0.10 (-0.72 to 0.94)	0.48 (0.05 to 0.91)	0.028	0.028	0.021 ^a
Tibia, T2 (ms)								
Lateral condyle								
Central	41.0 (8.3)	42.9 (8.1)	-0.66 (-1.86 to 0.45)	0.05 (-1.67 to 1.68)	0.15 (-0.28 to 0.58)	0.50	0.50	0.30 ^a
Medial condyle								
Central	44.5 (5.0)	42.7 (4.2)	-0.02 (-1.45 to 1.41)	-0.02 (-0.85 to 0.79)	-0.00 (-0.43 to 0.43)	1.00	1.00	0.41 ^a
Femur, dGEMRIC (ms)								
Lateral condyle								
Central	433 (70)	424 (44)	-4 (-16 to 7)	-1 (-11 to 8)	0.07 (-0.40 to 0.55)	0.77	0.77	0.93 ^b
Posterior	422 (60)	428 (57)	2 (-10 to 16)	6 (-8 to 22)	0.08 (-0.40 to 0.57)	0.72	0.72	0.71 ^b
Medial condyle								
Central	411 (61)	410 (65)	-19 (-32 to -6)	-6 (-17 to 7)	0.34 (-0.12 to 0.80)	0.14	0.14	0.13 ^b
Posterior	453 (60)	448 (61)	-23 (-39 to -8)	1 (-14 to 16)	0.53 (0.06 to 0.99)	0.022	0.022	0.022 ^b
Tibia, dGEMRIC (ms)								
Lateral condyle								
Central	424 (76)	419 (82)	-1 (-20 to 17)	1 (-15 to 17)	0.03 (-0.46 to 0.52)	0.91	0.91	0.95 ^b
Medial condyle								
Central	382 (75)	386 (50)	-20 (-35 to -6)	-6 (-20 to 8)	0.32 (-0.15 to 0.78)	0.19	0.19	0.09 ^b

T2 = transverse relaxation time; ^a Adjusted for baseline value, height and weight, dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage; ^b Adjusted for baseline value.

5.2.5 Training effects on physical performance and clinical symptoms

During four months of progressive aquatic resistance training, cardiorespiratory fitness VO_2 peak increased 9.8% in the training group and 4.4% in the control group (effect size: 0.58, 95%CI: 0.15 to 1.06, $p=0.010$ between groups). There were no between-group differences in the knee extension or flexion muscle force or in any domains of KOOS.

5.3 Self-assessed function and quality of life - 4-month RCT with 12-month follow-up

5.3.1 Drop-outs during the 12-month follow-up period

After the intervention study (Study I, $n=87$), 84 participants were willing to continue to the 12-month post-intervention follow-up study (Study II). During the 12-month follow-up period, seven participants dropped out of the study (2 intervention and 5 control). One participant died due to diagnosed cancer and one due to unknown reasons. In addition, one participant withdrew due to activated Ménière's disease, one due to personal reasons, one due to hip arthroplasty and one due to radiotherapy for breast cancer. Therefore 77 participants completed all follow-up measurements.

5.3.2 Short and long-term effects of training on self-assessed function and quality of life

After 4-months aquatic resistance training, there was a significant decrease in WOMAC stiffness domain -8.5mm (95%CI: -14.9 to -2.0, $p=0.006$) in the training group compared to controls (Figure 14). After the cessation of the training, this benefit was no longer observed in the 12-month follow-up. No between-group differences were observed in any domain of self-reported quality of life (SF-36) or the other domains of the WOMAC questionnaire at any measurement point.

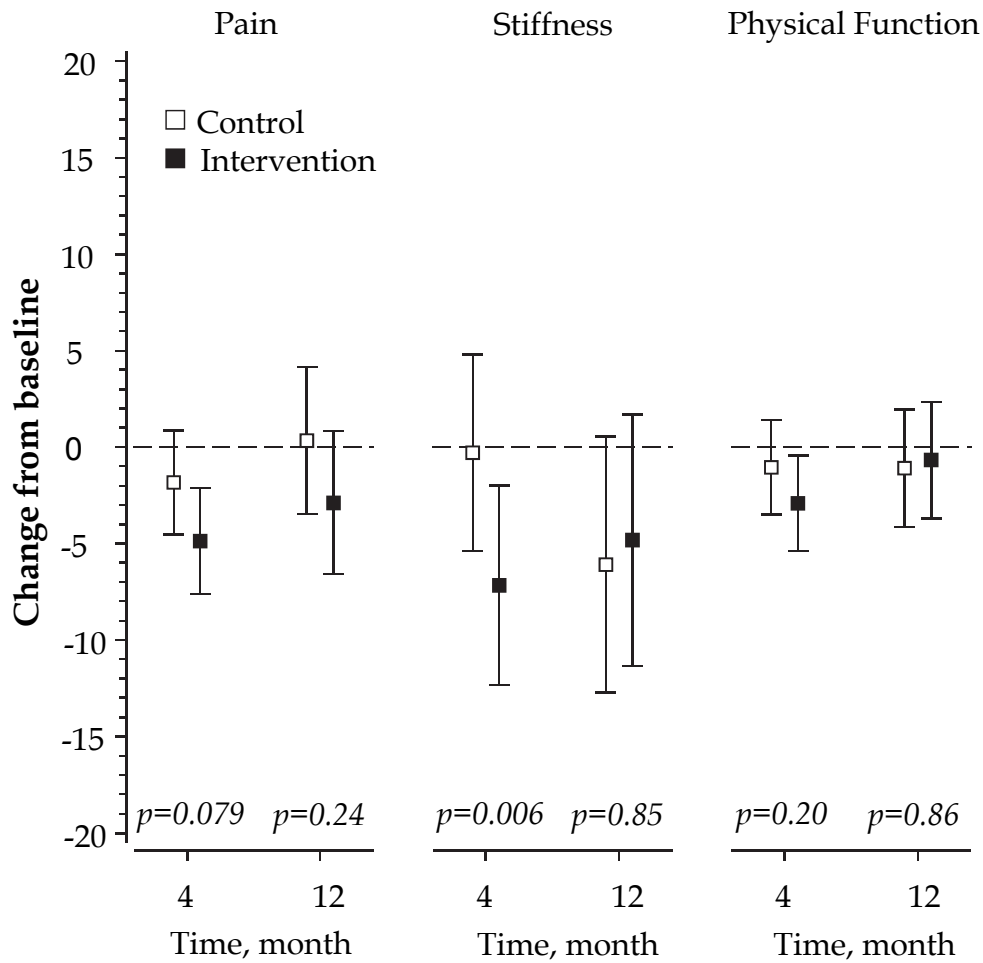


FIGURE 14 Short- and long-term effects of aquatic resistance training on self-assessed function (WOMAC).

5.4 Association between physical activity and cartilage quality

In addition to the drop-outs during the 12-month study period ($n=7$), one participant did not return the physical activity diaries from the entire follow-up period and was therefore dropped out from the analysis.

Thus, in total 76 participants were divided in tertiles based on their follow-up period LTPA (average monthly METH). The division into METH tertiles was: 1=lowest ($n=25$), 2=middle ($n=25$) and 3=highest ($n=26$). Importantly, there was no difference between the LTPA METH tertiles according to the original intervention study groups (i.e. members of the training and control group) in the beginning or during the follow-up (Table 7).

TABLE 7 Average monthly METH for the follow-up period.

	Lowest METH (n=25)	Middle METH (n=25)	Highest METH (n=26)
All participants			
METH, mean (SD)	52 (15)	97 (14)	155 (29)
Original intervention group			
Number (%)	16 (64.0)	12 (48.0)	11 (42.3)
METH, mean (SD)	53 (15)	96 (14)	156 (36)
Original control group			
Number (%)	9 (36.0)	13 (52.0)	15 (57.7)
METH, mean (SD)	49 (15)	98 (15)	155 (26)

Original intervention group: Intervention group of the original RCT design. Original control group: Control group of the original RCT design.

5.4.1 Feasibility of the cartilage analysis

One complete dGEMRIC index data set was not measured due to participant's rejection of contrast agent injection. Additionally, from the dGEMRIC index, 21 participants had movement artefact in the medial condyle, while in the lateral condyle, 17 participants had either artery-flow pulsating artefact or movement artefact and one inaccurate location of the slice compared to the baseline image. These data sets were therefore missing from the final analysis. In total 54 and 57 complete datasets for medial and lateral condyles respectively were available for quantitative dGEMRIC analysis.

5.4.2 The relationship between LTPA level and changes in estimated cartilage quality

In knee cartilage regions, there was a statistically significant linear relationship showing that dGEMRIC index in posterior ROI of the lateral ($p=0.003$) and medial ($p=0.006$) femoral cartilage increased with higher LTPA level during the 12-month period (Table 8). Furthermore, these changes were seen in the posterior lateral femoral cartilage superficial ($p=0.004$) and deep ($p=0.007$) ROIs and in the posterior medial superficial ROI ($p<0.001$) (Figure 15). No linear relationship was observed between LTPA level and changes in T2 relaxation time, physical performance characteristics or self-assessed impact of OA symptoms during the 12-month follow-up period.

TABLE 8 Cartilage trait value change during 12-month follow-up from different ROIs according to MET values.

	Change to month 12, mean (95% CI)			P for linearity
	Lowest METH (n=25)	Middle METH (n=25)	Highest METH (n=26)	
Femur, T2 (ms)				
Lateral condyle				
Central	0.29 (-1.23 to 1.54)	0.62 (-0.58 to 1.89)	-0.62 (-2.07 to 0.45)	0.79 ^a
Posterior	-0.97 (-2.17 to -0.003)	-1.29 (-2.47 to 0.002)	-0.87 (-2.20 to 0.32)	0.31 ^a
Medial condyle				
Central	-0.25 (-1.66 to 1.15)	-1.00 (-2.04 to -0.07)	-0.13 (-1.57 to 1.22)	0.89 ^a
Posterior	0.14 (-0.81 to 1.16)	-0.81 (-1.76 to 0.17)	0.05 (-0.86 to 0.95)	0.91 ^a
Tibia, T2 (ms)				
Lateral plateau				
Central	-1.24 (-3.40 to 0.72)	-0.77 (-2.50 to 0.87)	-0.25 (-1.96 to 1.30)	0.48 ^a
Medial plateau				
Central	-0.86 (-2.32 to 0.55)	-0.15 (-1.56 to 1.09)	-0.68 (-2.26 to 0.81)	0.97 ^a
Femur, dGEMRIC index (ms)				
Lateral condyle⁺				
Central	-8 (-22 to 5)	-14 (-31 to 4)	8 (-14 to 27)	0.16 ^b
Posterior	-17 (-32 to -2)	-8 (-35 to 12)	18 (-5 to 37)	0.003 ^b
Medial condyles[§]				
Central	-7 (-23 to 10)	12 (-7 to 27)	9 (-5 to 24)	0.12 ^b
Posterior	-17 (-39 to 6)	5 (-12 to 24)	24 (2 to 49)	0.006 ^b
Tibia, dGEMRIC index (ms)				
Lateral plateau				
Central	-8 (-24 to 9)	-22 (-44 to 1)	2 (-15 to 21)	0.07 ^b
Medial plateau				
Central	-17 (-34 to 4)	-13 (-42 to 11)	2 (-17 to 20)	0.16 ^b

T2 = transverse relaxation time; ^a adjusted for baseline value, height and weight, dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage; ^b adjusted for baseline value.

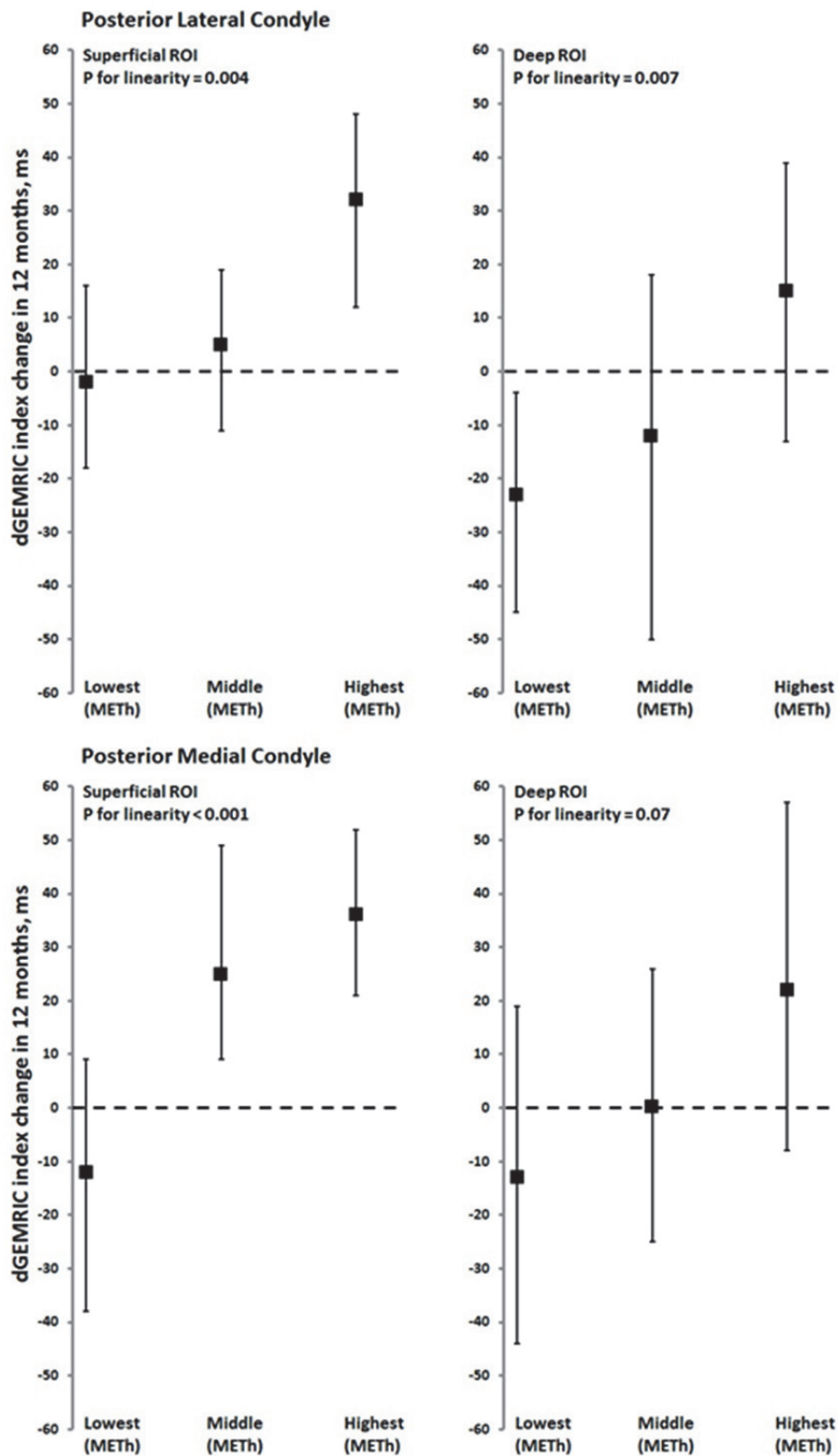


FIGURE 15 dGEMRIC index change during 12-month follow-up from femoral posterior lateral and medial superficial and deep ROI according to LTPA (METh) tertiles. METh = Average monthly Met hours. Highest = Highest tertile, Middle = Middle tertile, Lowest = Lowest tertile.

5.5 Neuromuscular performance as predictor of lower limb bone strength

Among the participants of the combined baseline data sets ($n=139$), counter movement jump peak power production was the strongest independent predictor for femoral neck Z ($\beta=0.44$; $p<0.001$) and for distal tibial BSI_d ($\beta=0.32$; $p=0.003$) in postmenopausal women with mild knee OA (Figure 16). This was also true in concentric net impulse for femoral neck Z ($\beta=0.37$; $p=0.001$) and for distal tibia BSI_d ($\beta=0.40$; $p<0.001$). Additionally, knee extension force ($\beta=0.30$; $p<0.001$) and figure-of-eight-running test ($\beta= -0.32$; $p<0.001$) were among strongest independent predictors for distal tibia BSI_d after adjustments. In figure-of-eight running test, faster time (thus negative value) predicts stronger bone. For tibial mid-shaft SSI_{maxmid} , concentric net impulse ($\beta=0.33$; $p=0.002$) remained as the strongest independent predictor after adjustments.

In those who had body composition measured (AquaRehab only, $n=87$), lean mass correlated with all bone strength indices, whereas fat mass did not. After Sidak adjustment, correlation between lean mass and femoral neck Z and tibial mid-shaft SSI_{maxmid} remained significant (Table 9).

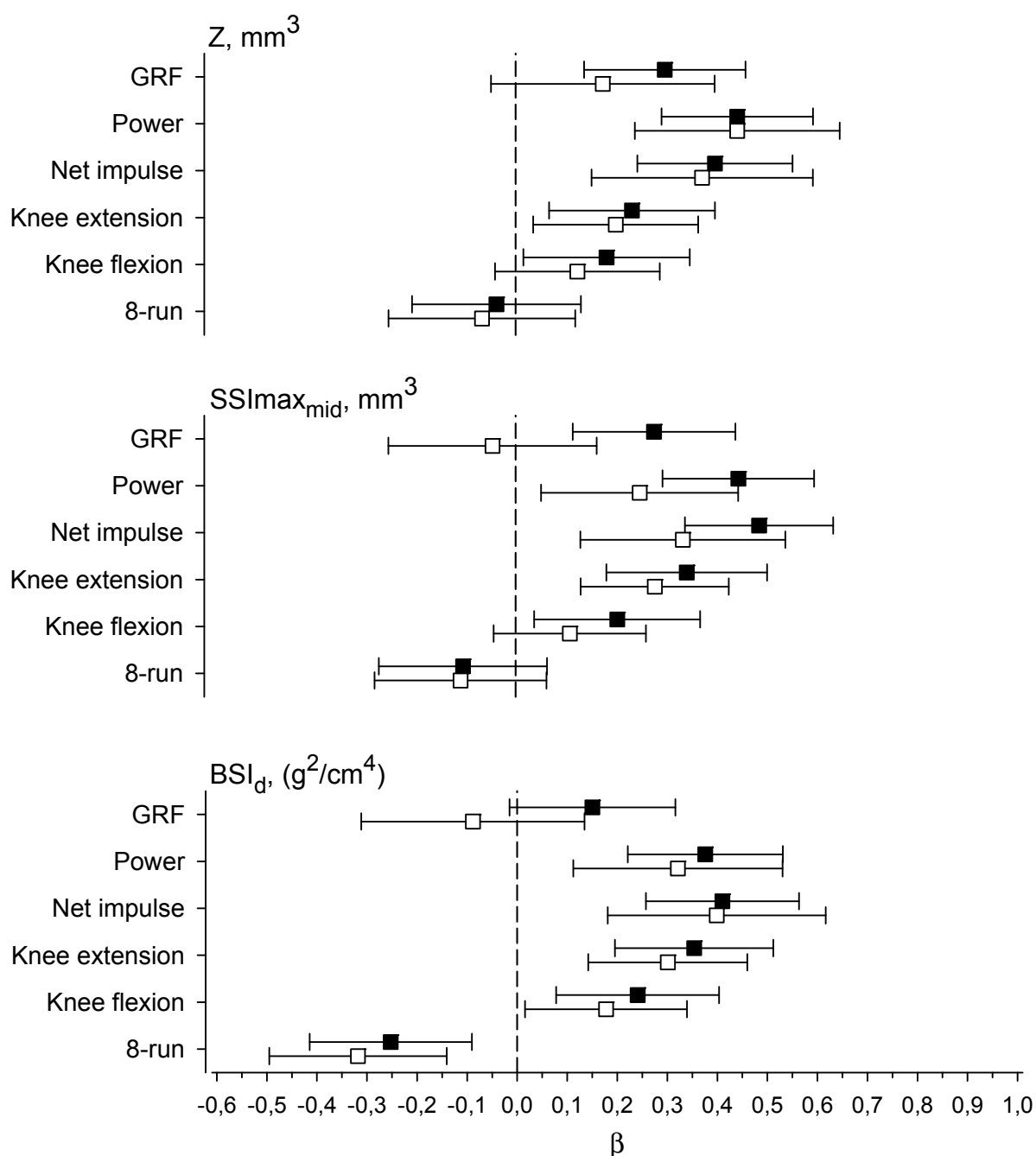


FIGURE 16 Univariate relationships between exercise related mechanisms and bone strength indices (β -values with 95% confidence intervals). ■ = crude and □ = height, weight and age adjusted bone strength indices. Z = femoral neck section modulus, SSImax_{mid} = tibial mid-shaft density weighted maximal moment of inertia, BSI_d = distal tibia compressive bone strength index, GRF = ground reaction force, Power = peak power production, Net impulse = concentric net impulse, Knee extension = knee extension force, Knee flexion = knee flexion force; 8-run = Figure-of-eight-running.

TABLE 9 Correlation coefficients (95% CI) between bone strength indices and body composition.

Bone strength indices of the lower limb	Lean mass	Fat mass
Femoral neck, Z (mm ³)	0.32 (0.11 to 0.51)*	0.08 (-0.14 to 0.29)
Tibial mid-shaft, SSImax _{mid} (mm ³)	0.53 (0.37 to 0.66)***	0.17 (-0.06 to 0.39)
Distal tibia, BSI _d (g ² /cm ⁴)	0.22 (0.03 to 0.38)	0.08 (-0.13 to 0.29)

Z = Femoral neck section modulus, SSImax_{mid} = tibial mid-shaft density weighted maximal moment of inertia, BSI_d = distal tibia compressive bone strength index.

Sidak adjusted probabilities: * p<0.05, ** p<0.001, *** p<0.001.

6 DISCUSSION

This study was conducted to examine the effects of 4-month progressive aquatic resistance training with 12-month follow-up and physical activity on knee articular cartilage in postmenopausal women with mild knee OA. Furthermore, the short-term effects (4-month) of the training on self-assessed function and quality of life and maintenance of possible benefits (12-month) were assessed. In addition, the relationship between lower limb neuromuscular performance and bone strength was studied.

The randomized controlled trial showed that the integrity of the collagen-interstitial water environment (T2) of the tibiofemoral cartilage may be responsive to low shear and compressive forces during aquatic resistance training, whereas further research is required to understand the exact nature of acute responses in dGEMRIC index to this type of loading. Also, aquatic resistance training improved cardiorespiratory fitness. As for the leisure-time physical activity, results suggest that the level of the activities is associated with beneficial regional changes in estimated knee articular cartilage quality (i.e. estimated GAG content) in 12 months, as measured with dGEMRIC index. After 4-months aquatic resistance training, there was a significant decrease in self-assessed stiffness of the knee in the training group compared to controls. After the cessation of the training, this benefit was not maintained on long-term. Moreover, the results of the cross-sectional study suggested that neuromuscular performance in postmenopausal women with mild knee OA predicted lower limb bone strength in every measured skeletal site.

6.1 Effects of exercise and physical activity on knee cartilage

Therapeutic aquatic exercise (TAE) is effective at managing symptoms and improving functional deficits in people with lower limb OA (Waller et al. 2014). Water is a facilitating environment in which persons with lower limb OA can

safely and comfortably exercise utilizing full joint range of motions not possible or normally recruited on land (Roper, Bressel & Tillman 2013). Due to the unique property of water causing reduced loading on the joint, the buoyancy (Harrison, Hillman & Bulstrode 1992), this modality has long been used as an effective and popular treatment option in this patient group. In this RCT study, we studied the efficacy of progressive, high volume aquatic resistance training on biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee OA. It has been thought that reduced loading due to buoyancy could protect the joints from further damage and allow more efficacious training for people who are unable to train effectively on land (Waller et al. 2014). To ensure maximal muscle contraction, intensity in our training program was at “as hard and fast as possible”. The average perceived exertion of the aquatic resistance training was RPE 15 (range, 12-17) and maximum heart rate was 144 (12) beats per minute. This combined with high training compliance (88%), training frequency (2.6x per week) and low dropout rate (n=1 per group) proves further that high intensity aquatic resistance training is both safe and suitable and it can be performed in high intensities in postmenopausal women with mild knee OA. Unlike in our exercise protocol, in our recent meta-analysis (Waller et al. 2014) it was found that previous TAE interventions have not had sufficient intensity or duration to cause physiological changes and the effects of TAE have been lost even at short-term.

This study showed concurrent responses in both T2 relaxation time and dGEMRIC index measuring the estimated biochemical composition of mildly osteoarthritic cartilage following four months of progressive aquatic resistance training in subjects with mild knee OA. These MRI methods provide unique and in-depth information on whether mildly osteoarthritic tibiofemoral cartilage is able to respond to mechanical loading over time. In a recently published systematic review (Bricca et al. 2017) it was concluded that moderate daily dose of exercise may have positive effects on cartilage matrix composition in healthy animals. Previous RCT studies on humans have shown that the mechanical loading created by the exercise interventions can have beneficial effects on the estimated biochemical composition of tibiofemoral (Roos & Dahlberg 2005) and patellofemoral (Koli et al. 2015) cartilage. Even though we found concurrent responses as a decrease both in T2 relaxation time and dGEMRIC index in the posterior region of medial femoral cartilage, our dGEMRIC results were in contrast with our T2 findings and the findings of Roos and Dahlberg (Roos & Dahlberg 2005). A decrease in T2 values is indicative of an improved integrity and orientation of the collagen fibres and a decrease in hydration of articular cartilage (Nieminen et al. 2001, Lammentausta et al. 2006), whereas decreases in dGEMRIC index values are associated with lower GAG content, i.e. degeneration of cartilage (Bashir et al. 1999, Nissi et al. 2004).

Aforementioned contrast between our results and a previous RCT study (Roos & Dahlberg 2005) can be explained at least partly by the older age of our study participants and the different stage of OA progression. Also, our observed decrease in dGEMRIC index values could suggest there was an in-

creased penetration of the contrast agent into the cartilage as a result of a decrease in GAG content within the cartilage matrix. There were no differences in physical activity between our training and control group other than the intervention and due to the non-impact nature of our training we question if there was a true decrease in GAG content. We could also speculate that our observed decrease in dGEMRIC index could be due to a reparative process within the cartilage as Bengtsson Moström et al. (2015) found a similar association in their cross-sectional study, i.e. lower T2 and dGEMRIC index was seen in the central ROI of the patella cartilage in young people with repetitive patella dislocation. Furthermore, our results could be partly explained by an increase in concentration of the contrast agent due to the reduction in cartilage hydration associated with a decrease in T2 (Li et al. 2010, Salo et al. 2012, Owman et al. 2014).

High repetition, low compression and shear cyclic forces with over 90 degrees knee flexion were achieved in our training at an abnormally high frequency. The mean number of repetitions completed per session with the affected leg was 481 (67), 416 (68) and 387 (58) for barefoot, small fins and large boots, respectively. 70.5% of these repetitions involved full knee active flexion and extension and thus produced contact between the posterior ROI of the femur and central tibia. It has been shown that when exposed to sufficient stimulus and environment, chondrocytes, including cells extracted from OA cartilage, have latent loading adaptation capacity to proliferate and regenerate matrix (e.g. GAGs and collagen) (Teichtahl et al. 2009, Jeon et al. 2013). Thus, the high number of repetitions together with low compression and shear cyclic forces from the aquatic resistance training might have caused positive responses in the articular cartilage in persons with mild knee OA. Also, the repetitive full ROM of the knee joint could have improved cartilage nutrition and removal of catabolites, therefore stimulating chondrocyte activity and improving and maintaining its biochemical properties (Arokoski et al. 2000, Wang et al. 2013).

The estimated biochemical composition of knee articular cartilage, both dGEMRIC index and T2 relaxation time, returned to baseline level after 12 months of cessation of the aquatic resistance training. During the intervention period, there were significant difference between the exercise and control group in average monthly LTPA due to the training. However, this difference was immediately lost after the cessation of the training (Waller et al. 2017). This suggests that the full ROM exercises created by aquatic resistance training had significant effect on the areas less loaded during normal activities of daily living. Furthermore, this suggests that in order to maintain cartilage quality, higher amounts of LTPAs are needed as it has been shown that the mechanical stress environment is an important factor that presumably regulates and influences the activity of the chondrocytes in vivo (Griffin & Guilak 2005).

As aquatic resistance training effects on knee articular cartilage returned to baseline level at 12-month follow-up, we found it important to observe in detail how LTPA is related to cartilage quality. Participants of the original intervention study were divided into MET task hour tertiles (lowest, middle, and highest) based on their monthly MET task hours. Based on the results of this

study we were able to conclude that in the 12-month follow-up period higher LTPA level was related to regional increases in estimated GAG content of tibio-femoral cartilage as measured with dGEMRIC index (Study III).

These regional changes were observed both in medial and lateral posterior ROI of the femoral condyle, further supporting our previous findings suggesting that daily less loaded posterior cartilage may have lower threshold for chondrocyte adaptation (Study I). These findings are also supported by several animal (Kiviranta et al. 1988, Kiviranta et al. 1994, Brismar et al. 2003) and human studies in healthy population (Tiderius et al. 2004, Teichtahl et al. 2009, Van Ginckel et al. 2010). Furthermore, physically active lifestyle has been associated with the maintenance of the biochemical properties of cartilage in people at high risk of developing knee OA after surgery for meniscal injury (Roos & Dahlberg 2005).

This linear relationship between LTPA changes and estimated knee cartilage quality was not observed in T2 relaxation time. These two MRI methods measure different cartilage attributes, indicating that the type of loading may affect different cartilage attributes. In our 4-month progressive resistance training program we found that full ROM knee movements with high repetition and compressive cyclic forces improved the estimated biochemical composition of the medial posterior femoral cartilage as measured with T2 (Study I). In contrast, the LTPAs may not have sufficient intensity and loading to cause adaptation in the integrity of the collagen-interstitial water environment (T2) whereas GAG concentration, i.e. dGEMRIC index, may be more responsive to loading created by LTPAs, i.e. intermittent impact and compression.

Walking (including Nordic walking) accounted for 40% of the total LTPA. The biomechanics of gait do not alone explain why the change in dGEMRIC index was observed in posterior ROI of the cartilage as it is less customary loaded during walking (Walker et al. 2001, Goyal et al. 2012). Intermittent impacts and loading during gait with higher LTPA level might have had favorable adjacent effects on less customary loaded posterior cartilage (e.g. trough pressure chances and muscle activation). Thus, the repetitive mechanical stimulus trough gait might have been sufficient enough to improve nutrient diffusion and fluid flow in the posterior ROI of the femoral cartilage. Furthermore, 23% of the activities accounted of the total LTPA were described as "other" (e.g. cleaning and gardening). These activities might have included nonrepetitive and higher knee ROMs (i.e. uncusomary loading) to the knee, which can be speculated to have had beneficial effect on less loaded posterior ROI of femoral cartilage.

Overall, chondrocytes in posterior region might have been more responsive to physical activities in posterior region of cartilage compared to central region chondrocytes as discussed in Study I. The chondrocytes in the central region of both femoral and tibia cartilage, i.e. a region loaded daily during normal locomotion, may require a higher or atypical load to stimulate an adaptive response.

6.2 Effects of exercise on physical performance, clinical symptoms and quality of life

We did not observe any significant changes in muscle force after 4-month aquatic resistance training. This result was in line with our recent systematic review showing no significant effect of TAE on muscle force (Waller et al. 2014). However, we performed isometric muscle testing, whereas the true muscle work during our intervention resembles to isokinetic strength testing more closely. Thus, isokinetic strength measurements could have been more sensitive to change.

This study showed significant improvement in cardiorespiratory fitness in favor of the aquatic resistance training group. This finding is supported by our previous study investigating the effects of TAE on aerobic fitness (Waller et al. 2014). Furthermore, it has been shown that the oxygen consumption (VO_2) is three times higher during aquatic treadmill running than on land (Becker 2009). Thus the same effect on aerobic capacity may be achieved with aquatic exercise with less exertion (Becker 2009), promoting water as a promising exercise environment which stimulates higher exercise efficiency with less exertion for people with painful joints and low physical activity level (Bartels et al. 2016).

There were no between-group differences in any of the domains of KOOS. Our study participants reported high values for KOOS at baseline, i.e. clinical symptoms were minor at baseline. Therefore this lack of significance was not a surprise. On the other hand, together with the results from physical performance, these results indicate that progressive aquatic resistance training had no harmful effects on clinical findings in this study population.

As discussed in Study I, Likert scale KOOS questionnaire was not sensitive enough to observe any between-group differences in any of the KOOS domains. Thus, VAS-scale WOMAC questionnaire could be more sensitive to the changes and give us deeper insight over OA-related symptoms. Further, OA-related pain and reduced physical function can culminate in reductions in quality of life (Fransen et al. 2015), making it an important factor in understanding OA as a whole. In this 4-month aquatic resistance training study with 12-month follow-up, there was a significant decrease in WOMAC knee stiffness in the training group compared to controls. During the intervention, full knee range of motion was ensured, whereas gait on level surface requires knee ROM from nearly full extension to 60-65 degree flexion (Walker et al. 2001). During the intervention period, there was a significant between-group difference between study groups in average monthly LTPA due to aquatic resistance training. However, this difference was immediately lost after the cessation of the aquatic resistance training (Waller et al. 2017). This might partly explain why the improvements in knee stiffness were no longer seen at the 12-month follow-up as the former participants of the intervention group went back to their normal level and type of leisure time physical activities. As mentioned earlier, most common LTPA during the follow-up period was walking, which does not require

full range knee motions as described above. This finding is also in line with our previous systematic review showing that directly after intervention, TAE had a small, but significant effect on knee stiffness (Waller et al. 2014). Furthermore, there was a trend, though not statistically significant, showing a possible pain reduction in aquatic resistance training group, which might partly support the found reduction in knee stiffness.

Contrary to previous systematic reviews of TAE (Waller et al. 2014) and land-based therapeutic exercise in osteoarthritic population (Fransen et al. 2015), no between-group differences were observed in any of the quality of life questionnaire (SF-36) domains. The effect size was found to be small in both studies and caution in interpretation of the results was noticed. The outcome measures used may not accurately represent the true changes in the QOL in these patients as involved studies used a variety of continuous scales to evaluate quality of life outcomes (Waller et al. 2014, Fransen et al. 2015) and the number of included studies in TAE (Waller et al. 2014) and land-based exercise (Fransen et al. 2015) systematic reviews were relatively low (8 and 13 respectively). Furthermore, as was the case with the KOOS values at baseline, high SF-36 values were reported at baseline, leaving little room for possible positive changes. On the other hand, as found in KOOS pain dimension, there was also a trend, though not significant, showing a possible bodily pain reduction in SF-36.

In the 12-month follow-up, studying how LTPA is related with cartilage quality, cardiorespiratory fitness, muscle force and all KOOS dimensions remained at the follow-up initiation level, and no linearity with LTPA tertiles was observed during the 12 months. Importantly, even at the highest level LTPA was well tolerated and did not increase clinical symptoms.

6.3 Neuromuscular performance as predictor of lower limb bone strength

In Study IV, we found that neuromuscular performance predicted bone strength along the lower limb at the femoral neck, tibial mid-shaft and distal tibia so that the better the neuromuscular performance was the higher the bone strength was. Strongest predictors of the lower limb bone strength indices were peak power production during counter movement jump, concentric net impulse, knee extension force and figure-of-eight-running. This finding is in line with a previous study (Khan 2001) showing that the highest measurable strain during running occurs at the distal tibia and calcaneus with the greatest strain being generated at the cortex under compression.

It has been suggested that there is an inverse relationship between mild knee OA and osteoporosis (OP), i.e. OA would have protective effect against OP (Sowers et al. 1999, Multanen et al. 2015). However, it has been shown that when the disease progresses, OA would lose the protective effect for some rea-

son (Chang et al. 2014). Also, in a recent study, weak to moderate but significant correlations were found showing that when tibial cartilage is degenerated, the underlying tibial bone structure, i.e. subchondral bone, is also deteriorated (Hirvasniemi et al. 2017).

Furthermore, it has been shown that falling is the strongest single risk factor for fractures, not OP (Kannus et al. 2005, van Helden et al. 2008). Regular exercise increases daily physical activity and decreases risk of falling in OA patients (Bennell & Hinman 2011). In a recent cohort study with almost 70000 individuals was shown that people who reported exercise 1 hour per week had a lower rate of hip fracture and any fracture compared with those who exercised less than 1 hour per week (Stattin et al. 2017). In addition, there is a consistent doubling of fracture risk for each SD reduction in BMD, irrespective of BMD measurement site and fracture type (Cefalu et al. 2004). Therefore, regular exercise can be recommended as a means to improve skeletal as well as cartilage health and should be investigated in more detail as the effects of physical exercise on human cartilage and subchondral bone are poorly understood and we do not know the specific type, intensity and amount of exercise that would be optimal for the joint.

6.4 Methodological considerations

This dissertation is mainly based on findings from a large RCT study project (AquaRehab). The main aim of the project was to investigate the effects of high intensity aquatic resistance training on estimated biochemical composition of the knee cartilage in postmenopausal women. Additionally, a cross-sectional study implementing combined data set of two large RCT projects (AquaRehab and LuRu), assessing the association between neuromuscular performance and lower limb bone strength traits, was conducted. Eligibility criteria in these two RCTs were otherwise similar except for age (AquaRehab age range: 60 – 68 years and LuRu: 50 - 66 years) and for BMI (AquaRehab: ≤ 34 kg/m² and LuRu: ≤ 35 kg/m²). Measurement protocols were similar in both studies except for measured leg in pQCT. In LuRu study, right leg was always measured whereas in AquaRehab study, images were taken from the affected knee side leg (i.e. higher knee K/L graded side). Thus, only participants from LuRu who had higher K/L grading in their right knee were included in Study IV.

6.4.1 Strengths and limitations of the MRI and follow-up studies (Studies I, II and III)

The strengths of the intervention studies include the high adherence to a highly intensive aquatic resistance training program with a small number of drop-outs. These strengths indicate that postmenopausal women with mild knee OA were

able to withstand progressive aquatic resistance training and they were highly motivated. AquaRehab study was the first study to record leisure time physical activities throughout the whole 4-month intervention (in addition to the aquatic exercise) and a 12-month follow-up period. Thus, due to this control for confounding factor, intervention studies (Study I and II) were able to demonstrate the true effects of progressive aquatic resistance training. These studies were designed to fulfill all the important quality criteria in RCT, except for blinding the participants to exercise therapy, which is common in exercise therapy studies (Furlan et al. 2009). Further, the strengths of the LTPA study (Study III) include the long-term follow-up period (12 months) and high adherence to the end measurements with no harms observed as LTPA level increased.

Due to the strict inclusion criteria in the original intervention study (Study I and II), the study sample was homogeneous. Therefore, the results of this dissertation cannot be directly applied to people with progressed OA or older or extremely obese women and men. This study had multiple endpoints and therefore results have to be viewed with caution. All p-values and CI's are quoted, rather than presenting the potential errors and problems associated with formal adjustments for potential multiplicity issues.

The intensity of aquatic resistance training (Study I and II) was monitored through heart rates, RPE and blood lactates (Waller et al. 2017). Due to this indirect measurement, we were not able to control the exact work done by the lower limb muscles. Furthermore, LTPA was evaluated subjectively with diaries (Study III). This might have led to overestimation of the daily physical activities and lost data due to unmarked activities. Additionally, two assessors (MM, author of the dissertation, and BW, responsible for aquatic resistance training) were not blinded to the study.

Cartilage and imaging

Strict imaging procedures and segmentation rules were used in both MRI studies (Studies I and III) to ensure good stability and repeatability of the T2 and dGEMRIC indices. Nevertheless, this did not rule out, the possibility that the results of the MRI indices are affected by the magic angle (particularly T2) and partial volume effects (Hannila et al. 2015). The long imaging time in dGEMRIC mapping might result in motion artefact which was controlled for in our study by using a motion correction technique built into the in-house software, as well as strict inclusion/exclusion criteria for image quality.

MRI imaging performed with a 1.5 tesla scanner, whereas a 3.0 tesla scanner would have produced better spatial resolution and higher signal-to-noise ratio. The mean changes seen in T2 and dGEMRIC index fall within the upper limits of our measurement error for both techniques. Therefore, we cannot exclude measurement error as a possible explanation for our findings. In some cases, occasionally thinned and deteriorated cartilage and movement or pulsating artery artefact prevented reliable segmentation of cartilage resulting in lost data. Also, we used single-slice segmenting method assessing articular cartilage, whereas multi-slice method might have produced more a comprehensive view

of the knee cartilage. The MRI analysis application divided cartilage to deep and superficial compartments (50%/50%) and due to the 1.5T scanner used, segmented cartilage thickness was from two to five voxels reducing the spatial accuracy. Therefore, care should be taken when interpreting these results. Pre-contrast T1 imaging was not used in this study. However, its importance has been questioned and we think that this omission does not affect our conclusions (Li et al. 2009, Hawezi et al. 2011).

Classification of OA severity was performed using a combination of pain and Kellgren-Lawrence classification (weight-bearing) and therefore it was not possible to differentiate between healthy and biochemically altered cartilage between ROIs and condyles (Multanen et al. 2015). It is still unknown if an aquatic training program of longer than four months would have created a global response throughout the cartilage. It is plausible to hypothesize that as cartilage health in one ROI improves it may cause a positive response in adjacent ROIs.

Finally, so far there is no “golden standard” method to measure how exercise directly affects the biochemical composition of cartilage in vivo. Therefore, the different qMRI parameters and their interactions are not yet fully understood (Binks et al. 2013) and further investigations about the interaction between exercise, cartilage and these parameters are needed.

6.4.2 Strengths and limitations of the cross-sectional study (Study IV)

The strength of this study was bone strength indices being measured from several locations in the lower limb: femoral neck, tibial mid-shaft and distal tibia. However, knee and distal femur regions were not measured, which can be considered as a minor limitation. This study included only 50-68-year-old Caucasian females with mild knee OA recruited as part of the study groups of two larger randomized controlled trials with distinct inclusion/exclusion criteria, and thus results of the present study cannot be generalized to other groups. Furthermore, cross-sectional study design is not able to demonstrate causal relations. Therefore the findings remain purely hypothesis generating.

6.5 Implications and suggestions for future research

Short-term randomised controlled exercise intervention trials have shown to have a response in estimated tibiofemoral cartilage GAG concentration (Roos & Dahlberg 2005) (Study I). In our intervention study (Study I) we observed a decrease in dGEMRIC index after 4-month progressive aquatic resistance training in postmenopausal women with mild knee OA. Due to the lack of differences in physical activity, other than the intervention, there were no changes in self-reported symptoms (i.e. pain), and due to the non-impact nature of the inter-

vention implemented in the study, we suggested that there might be several reasons behind this phenomenon. Aquatic resistance training might have e.g. caused an acute initiation of reparative responses within the cartilage, rather than a true decrease in estimated GAG concentration (Study I). In contrast, Roos and Dahlberg (2005) found an increase in the dGEMRIC index, i.e. an increase in the estimated GAG concentration following a 4-month land-based neuromuscular training intervention in people at high risk of developing knee OA following surgery for meniscal injury. Furthermore, we observed in our long-term randomised controlled study (Multanen et al. 2014) that 12-month progressively implemented high-impact jumping training did not have a negative or positive effect on the biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee OA, but in the same study (Koli et al. 2015) found an improvement in the collagen matrix in the patella cartilage. Altogether, GAG concentration may be more responsive to intermittent impact and compression type of loading as seen by neuromuscular training in the study by Roos and Dahlberg (Roos & Dahlberg 2005) and by high LTPA level seen in our study. Also, low compression and shear forces in the aquatic program (Study I) may have been too low, and high-impact jumping training (Multanen et al. 2014) might have had too intense loading in order to provide an appropriate GAG stimulus. Thus, taken into account the results of the present study and previous randomised controlled trials, it is still unknown what type of exercise mode would be most optimal for improving cartilage quality in postmenopausal women with mild knee OA. At the moment there is no clear superiority between land-based strength versus aerobic training (Bennell & Hinman 2011, Uthman et al. 2013, Fransen et al. 2015) and also like land-based training, there is no consensus on what type of TAE is most effective in the management of lower limb OA (Waller et al. 2014). Also, outcomes following land-based and aquatic exercise appear to be comparable, making no training modality superior to other (Batterham, Heywood & Keating 2011). Finally, it is still unknown if any form of the exercise interventions actually is any better in maintaining cartilage health than active lifestyle (Study III).

As stated above, we cannot say based on the randomized controlled studies we have so far what is the best form (specific type, intensity and amount) of exercise or exercise induced loading for osteoarthritic human cartilage and subchondral bone. No form of exercise (neuromuscular, impact or aquatic) seems to be harmful for the estimated biochemical composition of knee cartilage and they all have some beneficial effects either on cartilage (Roos & Dahlberg 2005, Koli et al. 2015) (Study I) or bones (Multanen et al. 2014) as well as on variables in an exercise type depended manner (i.e. strength, aerobic, neuromuscular) and knee OA symptoms. Also, to date, studying a range of exercise loading, cartilage and subchondral bone has been difficult due to the challenges inherent in cartilage and subchondral bone qualitative and quantitative assessment as well as in the study design of the long-term randomized controlled exercise interventions.

One option for future research is to study which type of exercise and exercise induced loading is most effective for chondroprotection (i.e. able to prevent progression of OA) and subchondral bone in these study populations as diagnosed lower limb osteoarthritis can lead to activity avoidance. However, animal (Bricca et al. 2017) and RCT studies (Roos & Dahlberg 2005, Multanen et al. 2014, Koli et al. 2015) (Study I) clearly show the importance of exercise as part of the OA treatment chain. Therefore, maintenance of cartilage quality as chondroprotective (both GAG concentration and collagen network) means might be more important to study than most effective way to improve cartilage quality within this study population. Further investigations into the chondroprotective mechanisms, such as in different forms of exercise therapy, are likely to be highly informative and relevant, and ultimately will reveal novel therapeutic targets for OA treatments.

It has also been suggested that subchondral bone may be involved in OA development and that bone and cartilage are functionally coupled through either the distribution of joint loads or exchange of signalling molecules between the two adjacent tissues (Goldring & Goldring 2010). Subchondral bone provides a shock-absorbing and supportive function for the cartilage, and may also be important for cartilage metabolism (Imhof et al. 2000, Lories & Luyten 2011). Although the effect of exercise on bone has been extensively examined, hardly anything is known about the effect of exercise on subchondral bone in humans. Therefore, further understanding on the importance of different forms of therapeutic exercise and mechanical loading for articular cartilage, i.e., how loading can remodel cartilage and subchondral bone is needed. This will promote the present understanding to develop efficient, cost-effective and feasible pre-rehabilitation procedures to reduce the impact of OA and chronic lower limb joint symptoms.

7 MAIN FINDINGS AND CONCLUSIONS

The main findings of the study are as follows:

1. Progressive 4-month aquatic resistance training program causes regional adaptations in cartilage T2 relaxation time and dGEMRIC index and improves cardiorespiratory fitness in postmenopausal women with mild knee OA.
2. Progressive 4-month aquatic resistance training can alleviate self-assessed stiffness of the knee joint; however, this effect is not maintained long-term (12-months).
3. Higher LTPA level during a 12-month period is related to regional increases in the estimated GAG content of tibiofemoral cartilage as measured with the dGEMRIC index.
4. Neuromuscular performance traits predicted lower limb bone strength indices both in femur and in tibia. Also, lean body mass correlated significantly with femoral neck and tibial mid-shaft bending strength, whereas fat mass did not have correlation with bone strength indices.

In conclusion, the results of this study indicate that progressively implemented physical activities (i.e. aquatic resistance training or LTPAs) can cause regional adaptation in mildly osteoarthritic knee cartilage and a positive effect on cardiorespiratory fitness and self-assessed knee stiffness. Furthermore, progressively implemented physical activities are well tolerated, have high compliance and low risk of harm amongst postmenopausal women with mild knee OA. Better understanding of the effects of exercise on cartilage and subchondral bone is needed.

YHTEENVETO (FINNISH SUMMARY)

Liikunta polven nivelrikon hoidossa vaihdevuosi-ien ohittaneilla naisilla – vesivastusharjoittelun ja vapaa-ajan fyysisen aktiivisuuden vaikutukset satunnaistetussa kontrolloidussa tutkimuksessa.

Nivelrikko on maailman yleisin nivelsairaus joka edetessään heikentää yksilön toiminta- ja työkykyä sekä aiheuttaa kipua. Nivelrikon oireet kehittyvät hitaasti vuosien varrella ja n. 400 000 suomalaista kärsii polven tai lonkan nivelrikosta. Suomessa tehdään n. 12 000 tekonivelleikkausta vuosittain ja polven nivelrikolla on 83%:n osuus kaikista nivelrikon kokonaiskustannuksista ja näin ollen sillä on merkittävät sosioekonomiset kustannukset maailmanlaajuisesti. Polven nivelrikon etenemiselle on ominaista nivelruston rappeutuminen, nivelen sisäinen tulehdus ja muutokset ruston alaisessa luussa. Lisäksi alkavassa polven nivelrikossa tapahtuu muutoksia nivelruston biokemiallisessa koostumuksessa, mm. ruston glykosaminoglykaanin määrä alenee.

Vaikka nivelrikkoon ei ole tunnettua parantavaa hoitomuotoa, pystytään sen oireita vähentämään taudin varhaisissa vaiheissa. Tieteelliseen näyttöön perustuvat kliiniset ohjeistukset suosittelevat painonpudotusta, liikuntaa ja tautiin liittyvää koulutusta nivelrikon varhaisina hoitomuotoina. Polven nivelrikon hoidosta on myös olemassa positiivista tutkimusnäyttöä liike- ja liikuntaharjoittelun vaikuttavuudesta kipuun, toimintakykyyn ja elämänlaatuun riippumatta harjoittelutyypistä (aerobinen tai voimaharjoittelu) tai onko harjoittelu suoritettu vedessä tai maalla. Myös polven nivelruston biokemiallisia ominaisuuksia voidaan ylläpitää aktiivisella, liikuntaa sisältävällä elämäntyyllillä. Merkittävää on myös, että polven nivelrustoa tutkivissa satunnaistetuissa kontrolloiduissa tutkimuksissa ei ole havaittu polven nivelrustoa haittaavia vaikutuksia ja harjoittelu on kovasta intensiteetistä huolimatta hyvin siedettyä. Tämän väitöskirjatutkimuksen päätavoitteena oli selvittää progressiivisen neljä kuukautta kestäneen vesivastusharjoittelun vaikutuksia polven nivelruston kemialliseen koostumukseen, fyysiseen toimintakykyyn, nivelrikon oireisiin ja elämänlaatuun. Lisäksi tutkittiin 12 kuukauden vapaa-ajan fyysisen aktiivisuuden ja polven nivelruston koostumuksen välisiä yhteyksiä vaihdevuosi-ien ohittaneilla naisilla, joilla oli radiologisesti todettu lievä polven nivelrikko. Lisäksi tarkoituksena oli tutkia, ennustaako alaraajojen fyysinen suorituskyky reisi- ja sääri- luun lujutta.

Satunnaistettuun kontrolloituun vesivastusharjoittelututkimukseen osallistui 87 lievää polvennivelrikkoa sairastavaa 60-68 vuotiasta naista (Tutkimukset I-II). Tutkittavat satunnaistettiin harjoitteluryhmään (n = 43) ja ei harjoittelemaan kontrolliryhmään (n = 44). Harjoittelun vaikutuksia polven nivelruston biokemialliseen koostumukseen arvioitiin ruston kuvantamiseen kehitetyillä T2 relaksaatioaika- ja dGEMRIC-magneettikuvauksella. Lisäksi selvitettiin harjoittelun vaikutuksia maksimaaliseen hapenottokykyyn, isometriseen polven ojennus- ja koukistusvoimaan sekä itsearvioituihin nivelrikon oireisiin. Tutkimuksessa II tutkittiin lisäksi elämänlaatua. Neljä kuukautta kestänyt vesivastushar-

joittelu suoritettiin Telkänpesän Palvelukeskuksen terapia-altaalla Jyväskylässä. Tutkimuksen mittaukset suoritettiin Jyväskylän yliopiston liikuntatieteellisen tiedekunnan tiloissa. Röntgen- ja magneetikuvantaminen tapahtui Keski-Suomen keskussairaalassa. Osa tulosanalyyseistä suoritettiin yhteistyössä Oulun yliopistollisen sairaalan radiologian klinikan sekä Oulun yliopiston lääketieteen tekniikan laitoksen kanssa.

Tässä 12 kuukauden vapaa-ajan fyysisen aktiivisuuden ja nivelruston koostumuksen yhteyksiä havainnoivassa tutkimuksessa 76 tutkittavaa jaettiin kolmeen ryhmään perustuen heidän vapaa-ajan fyysiseen aktiivisuustasoonsa 12 kuukauden ajalta: 1. korkea (n=26), 2. kohtuullinen (n=25) ja 3. matala (n=26) (Tutkimus III). Tutkittavat täyttivät päivittäin liikuntapäiväkirjaa koko tutkimusjakson ajan. Vapaa-ajan fyysisen aktiivisuustason yhteyttä polven nivelruston laatuun, fyysistä suorituskykyä sekä itsearvioituja oireita arvioitiin edellä mainituilla menetelmillä.

Alaraajojen fyysistä suorituskykyä ja alaraajan luun lujuutta havainnoivassa poikkileikkaustutkimuksessa (Tutkimus IV) hyödynnettiin yhdistettyä vesivastusharjoitteluaineistoa ja aikaisemman LuRu -tutkimuksen aineistoa. Tutkimukseen osallistui yhteensä 139 lievää polvennivelrikkoa sairastavaa 50-68 vuotiasta naista. Alaraajojen fyysistä suorituskykyä mitattiin maksimaalisella esikevennyshyppyllä, isometrisellä polven ojennus- ja koukistusvoimalla ja kahdeksikkojuoksulla. Reisiluun kaulan sekä säären keski- ja alaosan luun lujuutta mitattiin tietokonetomografialla.

Neljä kuukautta kestäneen harjoittelun tulokset osoittivat, että progressiivinen vesivastusharjoittelu aiheuttaa merkitseviä alueellisia muutoksia polven nivelrustossa verrattuna kontrolliryhmään. Lisäksi vesivastusharjoittelu paransi merkitsevästi maksimaalista hapenottokykyä ja itsearvioitua polven jäykkyyttä. Harjoittelu oli hyvin siedettyä, osallistumisprosentti oli korkea (88%) ja poispuodonneiden määrä oli alhainen (2 henkilöä, 2,3%). Näiden tulosten perusteella progressiivinen vesivastusharjoittelu näyttäisi soveltuvan henkilöille, joilla on lievä polven nivelrikko. Lisätutkimuksia vaaditaan akuuttien polven nivelruston biokemiallisten muutosten ymmärtämiseksi.

Tulokset vapaa-ajan fyysisen aktiivisuuden ja nivelruston koostumuksen yhteyksistä osoittivat, että korkeammalla vapaa-ajan fyysisellä aktiivisuustasolla oli tilastollisesti merkitsevä lineaarinen yhteys polven nivelruston arvioidun biokemiallisen koostumuksen kanssa 12 kuukauden seurantajakson jälkeen. Liikuntapäiväkirjojen palautusprosentti oli korkea (97,4%). Seurannasta poissaoloneita oli kahdeksan (10%). Näiden tulosten perusteella korkeampi vapaa-ajan fyysinen aktiivisuus pystyi tuottamaan riittävästi ärsykeitä, jotka paransivat polven nivelruston arvioitua biokemiallista koostumusta. Nämä tulokset ovat merkittäviä, kun määritetään fyysisen aktiivisuuden tasoja nivelruston laatuun liittyvissä tutkimuksissa kuin myös nivelrikon kliinisessä kuntoutuksessa.

Alaraajojen fyysisen suorituskyvyn ja alaraajan luun lujuuden välisiä yhteyksiä tarkastelevan poikkileikkauksen tulokset osoittivat, että alaraajojen fyysinen suorituskyky ennusti luun lujuutta kaikilla mitatuilla alueilla. Nämä tu-

lokset tuottavat uutta ja merkityksellistä tietoa kun ennustetaan suorituskyvyn ja luun lujuuden välisiä yhteyksiä. Nämä tulokset antavat myös tärkeää ja arvokasta tietoa kun suunnitellaan tarkoituksenmukaista sisältöä luuterveyteen liittyviin tutkimuksiin kuin myös interventiotutkimuksiin vaihdevuosi-ikä ohittaneilla naisilla, joilla on lievä polven nivelrikko.

REFERENCES

- Ainsworth, B. E., Haskell, W. L., Herrmann, S. D., Meckes, N., Bassett, D. R., et al. 2011. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Medicine and science in sports and exercise* 43 (8), 1575-1581.
- Altman, R., Asch, E., Bloch, D., Bole, G., Borenstein, D., et al. 1986. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. *Arthritis and Rheumatism* 29 (8), 1039-1049.
- Andriacchi, T. P., Briant, P. L., Bevill, S. L. & Koo, S. 2006. Rotational changes at the knee after ACL injury cause cartilage thinning. *Clinical orthopaedics and related research* 442, 39-44.
- Andriacchi, T. P., Koo, S. & Scanlan, S. F. 2009. Gait Mechanics Influence Healthy Cartilage Morphology and Osteoarthritis of the Knee. *The Journal of Bone & Joint Surgery* 91 (Supplement_1), 95-101.
- Angele, P., Niemeyer, P., Steinwachs, M., Filardo, G., Gomoll, A., et al. 2016. Chondral and osteochondral operative treatment in early osteoarthritis. *Knee Surgery, Sports Traumatology, Arthroscopy* 24 (6), 1743-1752.
- Angst, F., Aeschlimann, A. & Stucki, G. 2001. Smallest detectable and minimal clinically important differences of rehabilitation intervention with their implications for required sample sizes using WOMAC and SF-36 quality of life measurement instruments in patients with osteoarthritis of the lower extremities. *Arthritis and Rheumatism* 45 (4), 384-391.
- Arokoski, J. P. A., Jurvelin, J. S., Väättäinen, U. & Helminen, H. J. 2000. Normal and pathological adaptations of articular cartilage to joint loading. *Scandinavian Journal of Medicine & Science in Sports* 10 (4), 186-198.
- Arokoski, J., Jurvelin, J., Kiviranta, I., Tammi, M. & Helminen, H. J. 1994. Softening of the lateral condyle articular cartilage in the canine knee joint after long distance (up to 40 km/day) running training lasting one year. *International Journal of Sports Medicine* 15 (05), 254-260.
- Arokoski, J., Manninen, P., Kröger, H., Heliövaara, M., Nykyri, E., et al 2007. Hip and knee pain and osteoarthritis. In L. Kaila-Kangas (Ed.) *Musculoskeletal Disorders and Diseases in Finland. Results of the Health 2000 Survey. Finland: Publications of the National Public Health Institute B25/2007*, 37-41.
- Bartels, E. M., Juhl, C. B., Christensen, R., Hagen, K. B., Danneskiold-Samsøe, B., et al. 2016. Aquatic exercise for the treatment of knee and hip osteoarthritis. *The Cochrane database of systematic reviews* 3, CD005523.
- Bashir, A., Gray, M. L., Hartke, J. & Burstein, D. 1999. Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. *Magnetic Resonance in Medicine* 41 (5), 857-865.
- Batterham, S. I., Heywood, S. & Keating, J. L. 2011. Systematic review and meta-analysis comparing land and aquatic exercise for people with hip or knee

- arthritis on function, mobility and other health outcomes. *BMC musculoskeletal disorders* 12 (1), 123.
- Becker, B. E. 2009. Aquatic therapy: scientific foundations and clinical rehabilitation applications. *American Academy of Physical Medicine and Rehabilitation* 1 (9), 859-872.
- Bellamy, N., Buchanan, W. W., Goldsmith, C. H., Campbell, J. & Stitt, L. W. 1988. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *The Journal of rheumatology* 15 (12), 1833-1840.
- Bellamy, N., Campbell, J., Robinson, V., Gee, T., Bourne, R., et al. 2005. Intraarticular corticosteroid for treatment of osteoarthritis of the knee. *The Cochrane database of systematic reviews* (2), CD005328.
- Bengtsson Moström, E., Lammentausta, E., Finnbogason, T., Weidenhielm, L., Janarv, P. M., et al. 2015. Pre- and postcontrast T1 and T2 mapping of patellar cartilage in young adults with recurrent patellar dislocation. *Magnetic resonance in medicine* 74 (5), 1363.
- Bennell, K., Hinman, R. S., Wrigley, T. V., Creaby, M. W. & Hodges, P. 2011. Exercise and osteoarthritis: cause and effects. *Comprehensive Physiology* 1 (4), 1943-2008.
- Bennell, K. L. & Hinman, R. S. 2011. A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. *Journal of Science and Medicine in Sport* 14 (1), 4-9.
- Bennell, K. L., Wrigley, T. V., Hunt, M. A., Lim, B. & Hinman, R. S. 2013. Update on the Role of Muscle in the Genesis and Management of Knee Osteoarthritis. *Rheumatic Diseases Clinics of North America* 39 (1), 145-176.
- Bennell, Hall, M. & Hinman, R. S. 2015. Osteoarthritis year in review 2015: rehabilitation and outcomes. *Osteoarthritis and Cartilage* 24 (1), 58-70.
- Berenbaum, F. 2012. Osteoarthritis as an inflammatory disease (osteoarthritis is not osteoarthrosis!). *Osteoarthritis and Cartilage* 21 (1), 16-21.
- Bijlsma, J. W., Berenbaum, F. & Lafeber, F. P. 2011. Osteoarthritis: an update with relevance for clinical practice. *Lancet (London, England)* 377 (9783), 2115-2126.
- Binks, D. A., Hodgson, R. J., Ries, M. E., Foster, R. J., Smye, S. W., et al. 2013. Quantitative parametric MRI of articular cartilage: a review of progress and open challenges. *The British journal of radiology* 86 (1023), 20120163.
- Brandt, K. D. 1999. Osteophytes in osteoarthritis. Clinical aspects. *Osteoarthritis and cartilage* 7 (3), 334-335.
- Bricca, A., Juhl, C.B., Grodzinsky, A. J. & Roos, E.M. 2017. Impact of a daily exercise dose on knee joint cartilage - a systematic review and meta-analysis of Randomized Controlled Trials in healthy animals. *Osteoarthritis and cartilage* 25 (8), 1223-1237.
- Brismar, B. H., Lei, W., Hjerpe, A. & Svensson, O. 2003. The effect of body mass and physical activity on the development of guinea pig osteoarthrosis. *Acta Orthopaedica Scandinavica* 74 (4), 442-448.

- Buckwalter, J. A. 2002. Articular cartilage injuries. *Clinical orthopaedics and related research* (402) (402), 21-37.
- Buckwalter, J. A. & Mankin, H. J. 1998. Articular cartilage: degeneration and osteoarthritis, repair, regeneration, and transplantation. *Instructional course lectures* 47, 487-504.
- Buckwalter, J. A., Mankin, H. J. & Grodzinsky, A. J. 2005. Articular cartilage and osteoarthritis. *Instructional course lectures* 54, 465-480.
- Buckwalter, J. A. & Martin, J. 1995. Degenerative joint disease. *Clinical symposia (Summit, N.J.: 1957)* 47 (2), 1-32.
- Buckwalter, J. A., Mow, V. C. & Ratcliffe, A. 1994. Restoration of Injured or Degenerated Articular Cartilage. *The Journal of the American Academy of Orthopaedic Surgeons* 2 (4), 192-201.
- Burstein, D. & Gray, M. 2003. New MRI techniques for imaging cartilage. *The Journal of bone and joint surgery. American volume* 85-A Suppl 2, 70.
- Cefalu, C. A. 2004. Is bone mineral density predictive of fracture risk reduction? *Current medical research and opinion* 20 (3), 341-349.
- Chang, C. B., Kim, T. K., Kang, Y. G., Seong, S. C. & Kang, S. 2014. Prevalence of Osteoporosis in Female Patients with Advanced Knee Osteoarthritis Undergoing Total Knee Arthroplasty. *Journal of Korean Medical Science* 29 (10), 1425-1431.
- Chen, T., Chen, L., Hsieh, M., Chang, C., Chou, D., et al. 2006. Evidence for a protective role for adiponectin in osteoarthritis. *BBA - Molecular Basis of Disease* 1762 (8), 711-718.
- Christensen, R., Astrup, A. & Bliddal, H. 2005. Weight loss: the treatment of choice for knee osteoarthritis? A randomized trial. *Osteoarthritis and cartilage* 13 (1), 20-27.
- Cirillo, D. J., Wallace, R. B., Wu, L. & Yood, R. A. 2006. Effect of hormone therapy on risk of hip and knee joint replacement in the Women's Health Initiative. *Arthritis and rheumatism* 54 (10), 3194-3204.
- Coggon, D., Croft, P., Kellingray, S., Barrett, D., McLaren, M., et al. 2000. Occupational physical activities and osteoarthritis of the knee. *Arthritis and rheumatism* 43 (7), 1443-1449.
- Cotofana, S., Ring-Dimitriou, S., Hudelmaier, M., Himmer, M., Wirth, W., et al. 2010. Effects of Exercise Intervention on Knee Morphology in Middle-Aged Women: A Longitudinal Analysis Using Magnetic Resonance Imaging. *Cells Tissues Organs* 192 (1), 64-72.
- Cross, M., Smith, E., Hoy, D., Nolte, S., Ackerman, I., et al. 2014. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Annals of the rheumatic diseases* 73 (7), 1323-1330.
- Dahlberg, L., Lammentausta, E., Tiderius, C. J. & Nieminen, M. T. 2012. In vivo monitoring of joint cartilage - lessons to be learned by delayed gadolinium enhanced magnetic resonance imaging of cartilage. *European musculoskeletal review* 7 (1) 58-62.

- Dayal, N., Chang, A., Dunlop, D., Hayes, K., Chang, R., et al. 2005. The natural history of anteroposterior laxity and its role in knee osteoarthritis progression. *Arthritis and rheumatism* 52 (8), 2343-2349.
- de Klerk, B. M., Schiphof, D., Groeneveld, Frans P. M. J, Koes, B. W., van Osch, Gerjo J. V. M, et al. 2009. No clear association between female hormonal aspects and osteoarthritis of the hand, hip and knee: a systematic review. *Rheumatology* 48 (9), 1160-1165.
- Dumond, H., Presle, N., Terlain, B., Mainard, D., Loeuille, D., et al. 2003. Evidence for a key role of leptin in osteoarthritis. *Arthritis and rheumatism* 48 (11), 3118-3129.
- Dunn, T. C., Lu, Y., Jin, H., Ries, M. D. & Majumdar, S. 2004. T2 relaxation time of cartilage at MR imaging: comparison with severity of knee osteoarthritis. *Radiology* 232 (2), 592-598.
- Eckstein, F., Hudelmaier, M. & Putz, R. 2006. The effects of exercise on human articular cartilage. *Journal of Anatomy* 208 (4), 491-512.
- Englund, M., Guermazi, A. & Lohmander, L. S. 2009. The meniscus in knee osteoarthritis. *Rheumatic diseases clinics of North America* 35 (3), 579-590.
- Englund, M., Guermazi, A., Gale, D., Hunter, D. J., Aliabadi, P., et al. 2008. Incidental Meniscal Findings on Knee MRI in Middle-Aged and Elderly Persons. *The New England Journal of Medicine* 359 (11), 1108-1115.
- Englund, M., Guermazi, A., Roemer, F. W., Aliabadi, P., Yang, M., et al. 2009. Meniscal tear in knees without surgery and the development of radiographic osteoarthritis among middle-aged and elderly persons: The Multicenter Osteoarthritis Study. *Arthritis and rheumatism* 60 (3), 831-839.
- Faraone, S. V. 2008. Interpreting estimates of treatment effects: implications for managed care. *Pharmacy and therapeutics* 33 (12), 700.
- Felson, D. T. & Zhang, Y. 1998. An update on the epidemiology of knee and hip osteoarthritis with a view to prevention. *Arthritis and Rheumatism* 41 (8), 1343-1355.
- Fernandes, L., Hagen, K. B., Bijlsma, J. W. J., Andreassen, O., Christensen, P., et al. 2013. EULAR recommendations for the non-pharmacological core management of hip and knee osteoarthritis. *Annals of the rheumatic diseases* 72 (7), 1125-1135.
- Fitzgerald, G. K., Piva, S. R. & Irrgang, J. J. 2004. Reports of joint instability in knee osteoarthritis: Its prevalence and relationship to physical function. *Arthritis Care & Research* 51 (6), 941-946.
- Fox, A. J. S., Bedi, A. & Rodeo, S. A. 2009. The Basic Science of Articular Cartilage: Structure, Composition, and Function. *Sports Health* 1 (6), 461-468.
- Fragonas, E., Mlynárik, V., Jellús, V., Micali, F., Piras, A., et al. 1998. Correlation between biochemical composition and magnetic resonance appearance of articular cartilage. *Osteoarthritis and Cartilage* 6 (1), 24-32.
- Fransen, M., McConnell, S., Harmer, A. R., Van der Esch, M., Simic, M., et al. 2015. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *British journal of sports medicine* 49 (24), 1554-1557.

- Furlan, A. D., Pennick, V., Bombardier, C., van Tulder, M. & Editorial Board, Cochrane Back Review Group 2009. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 34 (18), 1929-1941.
- Gegout, P. P., Francin, P., Mainard, D. & Presle, N. 2008. Adipokines in osteoarthritis: friends or foes of cartilage homeostasis? *Joint Bone Spine* 75 (6), 669-671.
- Glyn-Jones, S., Palmer, A. J., Agricola, R., Price, A. J., Vincent, T. L., et al. 2015. Osteoarthritis. *Lancet* (London, England) 386 (9991), 376-387.
- Goldring, M. B. & Goldring, S. R. 2010. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Annals of the New York Academy of Sciences* 1192 (1), 230-237.
- Goldring, M. B. & Goldring, S. R. 2007. Osteoarthritis. *Journal of Cellular Physiology* 213 (3), 626-634.
- Goyal, K., Tashman, S., Wang, J. H., Li, K., Zhang, X., et al. 2012. In Vivo Analysis of the Isolated Posterior Cruciate Ligament-Deficient Knee During Functional Activities. *The American Journal of Sports Medicine* 40 (4), 777-785.
- Griffin, T. M. & Guilak, F. 2005. The role of mechanical loading in the onset and progression of osteoarthritis. *Exercise and sport sciences reviews* 33 (4), 195-200.
- Grotle, M., Hagen, K. B., Natvig, B., Dahl, F. A. & Kvien, T. K. 2008. Obesity and osteoarthritis in knee, hip and/or hand: an epidemiological study in the general population with 10 years follow-up. *BMC musculoskeletal disorders* 9 (1), 132.
- Hall, B. K. 2005. *Bones and cartilage: developmental and evolutionary skeletal biology*. Academic Press.
- Hannila, I., Lammentausta, E., Tervonen, O. & Nieminen, M. 2015. The repeatability of T2 relaxation time measurement of human knee articular cartilage. *Magnetic Resonance Materials in Physics, Biology and Medicine* 28 (6), 547-553.
- Harrison, R., Hillman, M. & Bulstrode, S. 1992. Loading of the Lower Limb when Walking Partially Immersed: Implications for Clinical Practice. *Physiotherapy* 78 (3), 164-166.
- Hart, D. J. & Spector, T. D. 1993. The relationship of obesity, fat distribution and osteoarthritis in women in the general population: the Chingford Study. *The Journal of rheumatology* 20 (2), 331-335.
- Hawezi, Z. K., Lammentausta, E., Svensson, J., Roos, E. M., Dahlberg, L. E., et al. 2016. Regional dGEMRIC analysis in patients at risk of osteoarthritis provides additional information about activity related changes in cartilage structure. *Acta Radiologica* 57 (4), 468-474.
- Hawezi, Z. K., Lammentausta, E., Svensson, J., Dahlberg, L. E. & Tiderius, C. J. 2011. In vivo transport of Gd-DTPA2- in human knee cartilage assessed by depth-wise dGEMRIC analysis. *Journal of Magnetic Resonance Imaging* 34 (6), 1352-1358.

- Henriksen, M., Creaby, M. W., Lund, H., Juhl, C. & Christensen, R. 2014. Is there a causal link between knee loading and knee osteoarthritis progression? A systematic review and meta-analysis of cohort studies and randomised trials. *BMJ open* 4 (7), e005368.
- Heywood, S., McClelland, J., Geigle, P., Rahmann, A. & Clark, R. 2016. Spatiotemporal, kinematic, force and muscle activation outcomes during gait and functional exercise in water compared to on land: A systematic review. *Gait & Posture* 48, 120-130.
- Hinman, R. S., Heywood, S. E. & Day, A. R. 2007. Aquatic Physical Therapy for Hip and Knee Osteoarthritis: Results of a Single-Blind Randomized Controlled Trial. *Physical Therapy* 87 (1), 32-43.
- Hirvasniemi, J., Thevenot, J., Multanen, J., Haapea, M., Heinonen, A., et al. 2017. Association between radiography-based subchondral bone structure and MRI-based cartilage composition in postmenopausal women with mild osteoarthritis. *Osteoarthritis and cartilage* 25 (12), 2039-2046.
- Hochberg, M. C., Altman, R. D., April, K. T., Benkhalti, M., Guyatt, G., et al. 2012. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care & Research* 64 (4), 465-474.
- Holla, J. F., Dekker, J., Steultjens, M. P., Sanchez-Ramirez, D. C., Roorda, L. D., et al. 2014. The avoidance model in knee and hip osteoarthritis: a systematic review of the evidence. *Annals of the Rheumatic Diseases* 73 (6), 1220.
- Houard, X., Goldring, M. & Berenbaum, F. 2013. Homeostatic Mechanisms in Articular Cartilage and Role of Inflammation in Osteoarthritis. *Current Rheumatology Reports* 15 (11), 1-10.
- Hunter, D. J., Altman, R. D., Cicuttini, F., Crema, M. D., Duryea, J., et al. 2015. OARSI Clinical Trials Recommendations: Knee imaging in clinical trials in osteoarthritis. *Osteoarthritis and cartilage* 23 (5), 698-715.
- Hunter, D. J. & Felson, D. T. 2006. Osteoarthritis. *BMJ (Clinical research ed.)* 332 (7542), 639-642.
- Hyttinen, M. M., Arokoski, J. P. A., Parkkinen, J. J., Lammi, M. J., Lapveteläinen, T., et al. 2001. Age matters: collagen birefringence of superficial articular cartilage is increased in young guinea-pigs but decreased in older animals after identical physiological type of joint loading. *Osteoarthritis and Cartilage* 9 (8), 694-701.
- Imhof, H., Sulzbacher, I., Grampp, S., Czerny, C., Youssefzadeh, S., et al. 2000. Subchondral bone and cartilage disease: a rediscovered functional unit. *Investigative radiology* 35 (10), 581-588.
- Javaid, M. K., Kiran, A., Guermazi, A., Kwok, C. K., Zaim, S., et al. 2012. Individual magnetic resonance imaging and radiographic features of knee osteoarthritis in subjects with unilateral knee pain: the health, aging, and body composition study. *Arthritis and Rheumatism* 64 (10), 3246-3255.
- Jensen, L. K. 2008. Knee osteoarthritis: influence of work involving heavy lifting, kneeling, climbing stairs or ladders, or kneeling/squatting

- combined with heavy lifting. *Occupational and environmental medicine* 65 (2), 72-89.
- Jeon, J. E., Schrobback, K., Meinert, C., Sramek, V., Hutmacher, D. W., et al. 2013. Effect of Preculture and Loading on Expression of Matrix Molecules, Matrix Metalloproteinases, and Cytokines by Expanded Osteoarthritic Chondrocytes. *Arthritis & Rheumatism* 65 (9), 2356-2367.
- Jiang, L., Tian, W., Wang, Y., Rong, J., Bao, C., et al. 2011. Body mass index and susceptibility to knee osteoarthritis: A systematic review and meta-analysis. *Joint Bone Spine* 79 (3), 291-297.
- Johnson, V. L. & Hunter, D. J. 2014. The epidemiology of osteoarthritis. *Best Practice & Research: Clinical Rheumatology* 28 (1), 5-15.
- Juhl, C., Christensen, R., Roos, E. M., Zhang, W. & Lund, H. 2014. Impact of Exercise Type and Dose on Pain and Disability in Knee Osteoarthritis: A Systematic Review and Meta-Regression Analysis of Randomized Controlled Trials. *Arthritis & Rheumatology* 66 (3), 622-636.
- Kanis, J. A., McCloskey, E. V., Johansson, H., Odén, A., Melton, L. J., et al. 2008. A reference standard for the description of osteoporosis. *Bone* 42 (3), 467.
- Kannus, P., Sievänen, H., Palvanen, M., Järvinen, T. & Parkkari, J. 2005. Prevention of falls and consequent injuries in elderly people. *Lancet* 366 (9500), 1885-1893.
- Kellgren, J. H. & Lawrence, J. S. 1957. Radiological assessment of osteoarthrosis. *Annals of the Rheumatic Diseases* 16 (4), 494-502.
- Khan, K. 2001. *Physical activity and bone health*. Champaign, IL: Human Kinetics.
- Kiviranta, I., Tammi, M., Jurvelin, J., Arokoski, J., Saamanen, A. M., et al. 1994. Articular cartilage thickness and glycosaminoglycan distribution in the young canine knee joint after remobilization of the immobilized limb. *Journal of orthopaedic research: official publication of the Orthopaedic Research Society* 12 (2), 161-167.
- Kiviranta, I., Tammi, M., Jurvelin, J., Saamanen, A. M. & Helminen, H. J. 1988. Moderate running exercise augments glycosaminoglycans and thickness of articular cartilage in the knee joint of young beagle dogs. *Journal of orthopaedic research: official publication of the Orthopaedic Research Society* 6 (2), 188-195.
- Klussmann, A., Gebhardt, H., Nübling, M., Liebers, F., Quirós Perea, E., et al. 2010. Individual and occupational risk factors for knee osteoarthritis: results of a case-control study in Germany. *Arthritis research & therapy* 12 (3), R88.
- Knoop, J., van der Leeden, M., van der Esch, M., Thorstensson, C. A., Gerritsen, M., et al. 2012. Association of lower muscle strength with self-reported knee instability in osteoarthritis of the knee: Results from the Amsterdam Osteoarthritis Cohort. *Arthritis Care & Research* 64 (1), 38-45.
- Koli, J., Multanen, J., Häkkinen, A., Kiviranta, I., Kujala, U., et al. 2011. Reliability of the Finnish versions of WOMAC and KOOS forms for knee osteoarthritis. *Physiotherapy* 97 (Supp S1), D204.

- Koli, J., Multanen, J., Kujala, U., Häkkinen, A., Nieminen, M., et al. 2015. Effects of Exercise on Patellar Cartilage in Women with Mild Knee Osteoarthritis. *Medicine & Science in Sports & Exercise* 47 (9), 1767-1774.
- Kontulainen, S. A., Johnston, J. D., Liu, D., Leung, C., Oxland, T. R., et al. 2008. Strength indices from pQCT imaging predict up to 85% of variance in bone failure properties at tibial epiphysis and diaphysis. *Journal of musculoskeletal & neuronal interactions* 8 (4), 401.
- Kukkonen-Harjula, K., Laukkanen, R., Vuori, I., Oja, P., Pasanen, M., et al. 1998. Effects of walking training on health-related fitness in healthy middle-aged adults--a randomized controlled study. *Scandinavian Journal of Medicine & Science in Sports* 8 (4), 236-242.
- Kumppanina nivelriikko - näin tulen toimeen. Suomen Nivelyhdistys ry.
www.nivel.fi
- Lachance, L., Sowers, M., Jamadar, D., Jannausch, M., Hochberg, M., et al. 2001. The experience of pain and emergent osteoarthritis of the knee. *Osteoarthritis and Cartilage* 9 (6), 527-532.
- Lammentausta, E., Kiviranta, P., Nissi, M. J., Laasanen, M. S., Kiviranta, I., et al. 2006. T2 relaxation time and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) of human patellar cartilage at 1.5 T and 9.4 T: Relationships with tissue mechanical properties. *Journal of Orthopaedic Research* 24 (3), 366-374.
- Lange, A. K., Vanwanseele, B. & Fiatarone Singh, M. A. 2008. Strength training for treatment of osteoarthritis of the knee: a systematic review. *Arthritis and Rheumatism* 59 (10), 1488-1494.
- Lanyon, P., O'Reilly, S., Jones, A. & Doherty, M. 1998. Radiographic assessment of symptomatic knee osteoarthritis in the community: definitions and normal joint space. *Annals of the Rheumatic Diseases* 57 (10), 595-601.
- Lapveteläinen, T., Nevalainen, T., Parkkinen, J. J., Arokoski, J., Kiraly, K., et al. 1995. Lifelong moderate running training increases the incidence and severity of osteoarthritis in the knee joint of C57BL mice. *The Anatomical Record* 242 (2), 159-165.
- Laukkanen, R. M., Oja, P., Ojala, K. H., Pasanen, M. E. & Vuori, I. M. 1992. Feasibility of a 2-km walking test for fitness assessment in a population study. *Scandinavian journal of social medicine* 20 (2), 119-126.
- Laukkanen, R., Oja, P., Pasanen, M. & Vuori, I. 1992. Validity of a two kilometre walking test for estimating maximal aerobic power in overweight adults. *International journal of obesity and related metabolic disorders: journal of the International Association for the Study of Obesity* 16 (4), 263-268.
- Laukkanen, R., Oja, R., Pasanen, M. E. & Vuori, I. M. 1993. Criterion validity of a two-kilometer walking test for predicting the maximal oxygen uptake of moderately to highly active middle-aged adults. *Scandinavian Journal of Medicine & Science in Sports* 3 (4), 267-272.
- Lawrence, J. S., Bremner, J. M. & Bier, F. 1966. Osteo-arthritis. Prevalence in the population and relationship between symptoms and x-ray changes. *Annals of the rheumatic diseases* 25 (1), 1.

- Lespasio, M. J., Piuizzi, N. S., Husni, M. E., Muschler, G. F., Guarino, A., et al. 2017. Knee Osteoarthritis: A Primer. *The Permanente journal* 21, 183.
- Li, W., Du, H., Scheidegger, R., Wu, Y. & Prasad, P. V. 2009. Value of precontrast T(1) for dGEMRIC of native articular cartilage. *Journal of magnetic resonance imaging: Journal of magnetic resonance imaging* 29 (2), 494.
- Li, W., Scheidegger, R., Wu, Y., Edelman, R. R., Farley, M., et al. 2010. Delayed contrast-enhanced MRI of cartilage: Comparison of nonionic and ionic contrast agents. *Magnetic Resonance in Medicine* 64 (5), 1267-1273.
- Litwic, A., Edwards, M. H., Dennison, E. M. & Cooper, C. 2013. Epidemiology and burden of osteoarthritis. *British medical bulletin* 105 (1), 185-199.
- Loeser, R. F., Goldring, S. R., Scanzello, C. R. & Goldring, M. B. 2012. Osteoarthritis: A disease of the joint as an organ. *Arthritis and Rheumatism* 64 (6), 1697-1707.
- Lohmander, L. S., Englund, P. M., Dahl, L. L. & Roos, E. M. 2007. The Long-term Consequence of Anterior Cruciate Ligament and Meniscus Injuries. *The American Journal of Sports Medicine* 35 (10), 1756-1769.
- Lories, R. J. & Luyten, F. P. 2011. The bone-cartilage unit in osteoarthritis. *Nature reviews. Rheumatology* 7 (1), 43-49.
- Louboutin, H., Debarge, R., Richou, J., Selmi, T. A. S., Donell, S. T., et al. 2008. Osteoarthritis in patients with anterior cruciate ligament rupture: A review of risk factors. *The Knee*, 16 (4), 239-244.
- Lu, M., Su, Y., Zhang, Y., Zhang, Z., Wang, W., et al. 2015. Effectiveness of aquatic exercise for treatment of knee osteoarthritis. *Zeitschrift für Rheumatologie* 74 (6), 543-552.
- Lu, X., Sun, D., Guo, X., Chen, F., Lai, W., et al. 2004. Indentation Determined Mechanochemical Properties and Fixed Charge Density of Articular Cartilage. *Annals of Biomedical Engineering* 32 (3), 370-379.
- Lützner, J., Günther, K., Kirschner, S. & Kasten, P. 2009. Surgical options for patients with osteoarthritis of the knee. *Nature Reviews Rheumatology* 5 (6), 309-316.
- Makaram, N. & Clement, N. D. 2016. Osteoarthritis in obese populations: where are we now? *Annals of Joint* 1, 26.
- Mandelbaum, B. R., Browne, J. E., Fu, F., Micheli, L., Mosely, J. B., et al. 1998. Articular Cartilage Lesions of the Knee. *The American Journal of Sports Medicine* 26 (6), 853-861.
- Martin, J. & Buckwalter, J. 2002. Aging, articular cartilage chondrocyte senescence and osteoarthritis. *Biogerontology* 3 (5), 257-264.
- McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., et al. 2014. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis and Cartilage* 22 (3), 363-388.
- Messier, S. P., Mihalko, S. L., Legault, C., Miller, G. D., Nicklas, B. J., et al. 2013. Effects of Intensive Diet and Exercise on Knee Joint Loads, Inflammation, and Clinical Outcomes Among Overweight and Obese Adults With Knee

- Osteoarthritis: The IDEA Randomized Clinical Trial. *Journal of the American Medical Association* 310 (12), 1263-1273.
- Mosher, T. J., Liu, Y. & Torok, C. M. 2010. Functional cartilage MRI T2 mapping: evaluating the effect of age and training on knee cartilage response to running. *Osteoarthritis and Cartilage* 18 (3), 358-364.
- Multanen, J., Heinonen, A., Häkkinen, A., Kautiainen, H., Kujala, U. M., et al. 2015. Bone and cartilage characteristics in postmenopausal women with mild knee radiographic osteoarthritis and those without radiographic osteoarthritis. *Journal of musculoskeletal & neuronal interactions* 15 (1), 69.
- Multanen, J., Rauvala, E., Lammentausta, E., Ojala, R., Kiviranta, I., et al. 2009. Reproducibility of imaging human knee cartilage by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5 Tesla. *Osteoarthritis and Cartilage* 17 (5), 559-564.
- Multanen, J., Nieminen, M. T., Häkkinen, A., Kujala, U. M., Jämsä, T., et al. 2014. Effects of High-Impact Training on Bone and Articular Cartilage: 12-Month Randomized Controlled Quantitative MRI Study. *Journal of Bone and Mineral Research* 29 (1), 192-201.
- Neumann, D. A. 2002. *Kinesiology of the musculoskeletal system: Foundations for physical rehabilitation*. (1st edition) Mosby, St. Louis: USA.
- Newton, P. M., Mow, V. C., Gardner, T. R., Buckwalter, J. A. & Albright, J. P. 1997. Winner of the 1996 Cabaud Award. The effect of lifelong exercise on canine articular cartilage. *The American Journal of Sports Medicine* 25 (3), 282-287.
- Nguyen, U. D. T., Zhang, Y., Zhu, Y., Niu, J., Zhang, B., et al. 2011. Increasing prevalence of knee pain and symptomatic knee osteoarthritis: survey and cohort data. *Annals of internal medicine* 155 (11), 725.
- Nia, H. T., Bozchalooi, I. S., Li, Y., Han, L., Hung, H., et al. 2013. High-Bandwidth AFM-Based Rheology Reveals that Cartilage is Most Sensitive to High Loading Rates at Early Stages of Impairment. *Biophysical Journal* 104 (7), 1529-1537.
- Nieminen, M. T., Rieppo, J., Silvennoinen, J., Töyräs, J., Hakumäki, J. M., et al. 2002. Spatial assessment of articular cartilage proteoglycans with Gd-DTPA-enhanced T1 imaging. *Magnetic Resonance in Medicine* 48 (4), 640-648.
- Nieminen, M. T., Rieppo, J., Töyräs, J., Hakumäki, J. M., Silvennoinen, J., et al. 2001. T2 relaxation reveals spatial collagen architecture in articular cartilage: A comparative quantitative MRI and polarized light microscopic study. *Magnetic Resonance in Medicine* 46 (3), 487-493.
- Nieminen, M. T., Töyräs, J., Rieppo, J., Hakumäki, J. M., Silvennoinen, J., et al. 2000. Quantitative MR microscopy of enzymatically degraded articular cartilage. *Magnetic Resonance in Medicine* 43 (5), 676-681.
- Nissi, M. J., Töyräs, J., Laasanen, M. S., Rieppo, J., Saarakkala, S., et al. 2004. Proteoglycan and collagen sensitive MRI evaluation of normal and degenerated articular cartilage. *Journal of orthopaedic research: official publication of the Orthopaedic Research Society* 22 (3), 557-564.

- Øiestad, B. E., Juhl, C. B., Eitzen, I. & Thorlund, J. B. 2014. Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. *Osteoarthritis and Cartilage* 23 (2), 171-177.
- Owman, H., Tiderius, C. J., Ericsson, Y. B. & Dahlberg, L. E. 2014. Long-term effect of removal of knee joint loading on cartilage quality evaluated by delayed gadolinium-enhanced magnetic resonance imaging of cartilage. *Osteoarthritis and cartilage* 22 (7), 928-932.
- Palastanga, N., Field, D. & Soames, R. 2006. *Anatomy and human movement: structure and function.* (5th edition) Elsevier Health Sciences.
- Perel, P., Roberts, I., Sena, E., Wheble, P., Briscoe, C., et al. 2006. Comparison of treatment effects between animal experiments and clinical trials: systematic review. *BMJ* 334 (7586), 197-200.
- Polven ja lonkan nivelrikon fysioterapia. 2013. Suomen fysioterapeutit. http://www.terveysportti.fi/dtk/sfs/avaa?p_artikkeli=sfs00001
- Poole, A. R., Kojima, T., Yasuda, T., Mwale, F., Kobayashi, M., et al. 2001. Composition and structure of articular cartilage: a template for tissue repair. *Clinical orthopaedics and related research* 391 (391 Suppl), S33.
- Pöyhönen, T., Sipilä, S., Keskinen, K. L., Hautala, A., Savolainen, J., et al. 2002. Effects of aquatic resistance training on neuromuscular performance in healthy women. *Medicine and science in sports and exercise* 34 (12), 2103-2109.
- Pöyhönen, T., Keskinen, K. L., Hautala, A. & Mälkiä, E. 2000. Determination of hydrodynamic drag forces and drag coefficients on human leg/foot model during knee exercise. *Clinical Biomechanics* 15 (4), 256-260.
- Pöyhönen, T., Keskinen, K. L., Kyröläinen, H., Hautala, A., Savolainen, J., et al. 2001. Neuromuscular function during therapeutic knee exercise under water and on dry land. *Archives of Physical Medicine and Rehabilitation* 82 (10), 1446-1452.
- Rantalainen, T., Heinonen, A., Komi, P. & Linnamo, V. 2008. Neuromuscular performance and bone structural characteristics in young healthy men and women. *European Journal of Applied Physiology* 102 (2), 215-222.
- Rantalainen, T., Nikander, R., Heinonen, A., Multanen, J., Häkkinen, A., et al. 2010. Neuromuscular performance and body mass as indices of bone loading in premenopausal and postmenopausal women. *Bone* 46 (4), 964-969.
- Rinne, M., Pasanen, M., Vartiainen, M., Lehto, T., Sarajuuri, J., et al. 2006. Motor Performance in physically well-recovered men with traumatic brain injury. *Journal of Rehabilitation Medicine* 38 (4), 224-229.
- Rittweger, J., Schiessl, H., Felsenberg, D. & Runge, M. 2004. Reproducibility of the Jumping Mechanography As a Test of Mechanical Power Output in Physically Competent Adult and Elderly Subjects. *Journal of the American Geriatrics Society* 52 (1), 128-131.

- Roddy, E., Zhang, W. & Doherty, M. 2005. Aerobic walking or strengthening exercise for osteoarthritis of the knee? A systematic review. *Annals of the rheumatic diseases* 64 (4), 544-548.
- Rönn, K., Reischl, N., Gautier, E. & Jacobi, M. 2011. Current surgical treatment of knee osteoarthritis. *Arthritis* 2011, 454873.
- Roos, E. M. & Juhl, C. B. 2012. Osteoarthritis 2012 year in review: rehabilitation and outcomes. *Osteoarthritis and Cartilage* 20 (12), 1477-1483.
- Roos, E. M., Roos, H. P., Ekdahl, C. & Lohmander, L. S. 1998. Knee injury and Osteoarthritis Outcome Score (KOOS)--validation of a Swedish version. *Scandinavian Journal of Medicine & Science in Sports* 8 (6), 439-448.
- Roos, E. M. & Arden, N. K. 2016. Strategies for the prevention of knee osteoarthritis. *Nature reviews. Rheumatology* 12 (2), 92-101.
- Roos, E. M. & Dahlberg, L. 2005. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis and rheumatism* 52 (11), 3507-3514.
- Roper, J. A., MS, Bressel, E., EdD & Tillman, M. D., PhD 2013. Acute Aquatic Treadmill Exercise Improves Gait and Pain in People With Knee Osteoarthritis. *Archives of Physical Medicine and Rehabilitation* 94 (3), 419-425.
- Salo, E. N., Nissi, M. J., Kulmala, K. A., Tiitu, V., Töyras, J., et al. 2012. Diffusion of Gd-DTPA(2)(-) into articular cartilage. *Osteoarthritis and cartilage* 20 (2), 117-126.
- Schiphof, D., van den Driest & Runhaar, J. 2018. Osteoarthritis year in review 2017: rehabilitation and outcomes. *Osteoarthritis and cartilage* 26 (3), 326-340
- Segal, N. A. & Glass, N. A. 2011. Is quadriceps muscle weakness a risk factor for incident or progressive knee osteoarthritis? *The Physician and sportsmedicine* 39 (4), 44-50.
- Silverwood, V., Blagojevic-Bucknall, M., Jinks, C., Jordan, J. L., Protheroe, J., et al. 2015. Current evidence on risk factors for knee osteoarthritis in older adults: a systematic review and meta-analysis. *Osteoarthritis and Cartilage* 23 (4), 507-515.
- Sipilä, S., Multanen, J., Kallinen, M., Era, P. & Suominen, H. 1996. Effects of strength and endurance training on isometric muscle strength and walking speed in elderly women. *Acta Physiologica Scandinavica* 156 (4), 457-464.
- Skou, S. T. 2015. Pain and sensitization in knee osteoarthritis and persistent post-operative pain. Dissertation, Aalborg University.
- Song, Y., Greve, J. M., Carter, D. R. & Giori, N. J. 2008. Meniscectomy alters the dynamic deformational behavior and cumulative strain of tibial articular cartilage in knee joints subjected to cyclic loads. *Osteoarthritis and Cartilage* 16 (12), 1545-1554.
- Song, Y., Greve, J. M., Carter, D. R., Koo, S. & Giori, N. J. 2006. Articular cartilage MR imaging and thickness mapping of a loaded knee joint before and after meniscectomy. *Osteoarthritis and Cartilage* 14 (8), 728-737.

- Sowers, M., Lachance, L., Jamadar, D., Hochberg, M. C., Hollis, B., et al. 1999. The associations of bone mineral density and bone turnover markers with osteoarthritis of the hand and knee in pre- and perimenopausal women. *Arthritis and rheumatism* 42 (3), 483-489.
- Spector, T. D., Nandra, D., Hart, D. J. & Doyle, D. V. 1997. Is hormone replacement therapy protective for hand and knee osteoarthritis in women?: The Chingford Study. *Annals of the rheumatic diseases* 56 (7), 432-434.
- Srikanth, V. K., Fryer, J. L., Zhai, G., Winzenberg, T. M., Hosmer, D., et al. 2005. A meta-analysis of sex differences prevalence, incidence and severity of osteoarthritis. *Osteoarthritis and Cartilage* 13 (9), 769-781.
- Stattin, K., Michaelsson, K., Larsson, S. C., Wolk, A. & Byberg, L. 2017. Leisure-Time Physical Activity and Risk of Fracture: A Cohort Study of 66,940 Men and Women. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research* 32 (8), 1599-1606.
- Subburaj, K., Kumar, D., Souza, R. B., Alizai, H., Li, X., et al. 2012. The Acute Effect of Running on Knee Articular Cartilage and Meniscus Magnetic Resonance Relaxation Times in Young Healthy Adults. *The American Journal of Sports Medicine* 40 (9), 2134-2141.
- Tanaka, R., Ozawa, J., Kito, N. & Moriyama, H. 2013. Efficacy of strengthening or aerobic exercise on pain relief in people with knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Clinical Rehabilitation* 27 (12), 1059-1071.
- Teichtahl, A. J., Wluka, A. E., Forbes, A., Wang, Y., English, D. R., et al. 2009. Longitudinal effect of vigorous physical activity on patella cartilage morphology in people without clinical knee disease. *Arthritis and rheumatism* 61 (8), 1095-1102.
- Tiderius, C., Hori, M., Williams, A., Sharma, L., Prasad, P. V., et al. 2006. dGEMRIC as a function of BMI. *Osteoarthritis and cartilage* 14 (11), 1091-1097.
- Tiderius, C. J., Svensson, J., Leander, P., Ola, T. & Dahlberg, L. 2004. dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) indicates adaptive capacity of human knee cartilage. *Magnetic Resonance in Medicine* 51 (2), 286-290.
- Timmins, K. A., Leech, R. D., Batt, M. E. & Edwards, K. L. 2017. Running and Knee Osteoarthritis: A Systematic Review and Meta-analysis. *The American Journal of Sports Medicine* 45 (6), 1447-1457.
- Tortora, G. J. & Derrickson, B. H. 2006. *Principles of anatomy and physiology*. (11th edition) John Wiley & Sons. Hoboken, NJ.
- Torvinen, S., Kannu, P., Sievänen, H., Järvinen, T. A. H., Pasanen, M., et al. 2002. Effect of a vibration exposure on muscular performance and body balance. Randomized cross-over study. *Clinical physiology and functional imaging* 22 (2), 145-152.
- Uthman, O. A., van der Windt, Danielle A, Jordan, J. L., Dziedzic, K. S., Healey, E. L., et al. 2013. Exercise for lower limb osteoarthritis: systematic review

- incorporating trial sequential analysis and network meta-analysis. *BMJ: British Medical Journal* 347 (7928), 14.
- Uusi-Rasi, K., Rauhio, A., Kannus, P., Pasanen, M., Kukkonen-Harjula, K., et al. 2010. Three-month weight reduction does not compromise bone strength in obese premenopausal women. *Bone* 46 (5), 1286-1293.
- Vähä-Ypyä, H., Vasankari, T., Husu, P., Suni, J. & Sievänen, H. 2015. A universal, accurate intensity-based classification of different physical activities using raw data of accelerometer. *Clinical Physiology and Functional Imaging* 35 (1), 64-70.
- Valtonen, A., Pöyhönen, T., Heinonen, A. & Sipilä, S. 2009. Muscle Deficits Persist After Unilateral Knee Replacement and Have Implications for Rehabilitation. *Physical Therapy* 89 (10), 1072-1079.
- Valtonen, A., Pöyhönen, T., Sipilä, S. & Heinonen, A. 2010. Effects of aquatic resistance training on mobility limitation and lower-limb impairments after knee replacement. *Archives of Physical Medicine and Rehabilitation* 91 (6), 833-839.
- van der Esch, M., Knoop, J., Leeden, v. d., M, Voorneman, R., Gerritsen, M., et al. 2012. Self-reported knee instability and activity limitations in patients with knee osteoarthritis: results of the Amsterdam osteoarthritis cohort. *Clinical Rheumatology* 31 (10), 1505-1510.
- van der Esch, M., Holla, J. F., van der Leeden, M., Knol, D. L., Lems, W. F., et al. 2014. Decrease of Muscle Strength Is Associated With Increase of Activity Limitations in Early Knee Osteoarthritis: 3-Year Results From the Cohort Hip and Cohort Knee Study. *Archives of Physical Medicine and Rehabilitation* 95 (10), 1962-1968.
- Van Ginckel, A., Baelde, N., Almqvist, K. F., Roosen, P., McNair, P., et al. 2010. Functional adaptation of knee cartilage in asymptomatic female novice runners compared to sedentary controls. A longitudinal analysis using delayed Gadolinium Enhanced Magnetic Resonance Imaging of Cartilage (dGEMRIC). *Osteoarthritis and Cartilage* 18 (12), 1564-1569.
- van Helden, S., van Geel, A C M, Geusens, P. P., Kessels, A., Nieuwenhuijzen Kruseman, A. C., et al. 2008. Bone and Fall-Related Fracture Risks in Women and Men with a Recent Clinical Fracture. *The Journal of Bone & Joint Surgery* 90 (2), 241-248.
- van Meer, B. L., Meuffels, D. E., van Eijsden, W. A., Verhaar, J. A., Bierma-Zeinstra, S. M., et al. 2015. Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review. *British journal of sports medicine* 49 (15), 975-983.
- Van Rossom, S., Smith, C. R., Zevenbergen, L., Thelen, D. G., Vanwanseele, B., et al. 2017. Knee Cartilage Thickness, T1ρ and T2 Relaxation Time Are Related to Articular Cartilage Loading in Healthy Adults. *PLoS One* 12 (1), e0170002.
- Vincent, H. K., Heywood, K., Connelly, J. & Hurley, R. W. 2012. Obesity and weight loss in the treatment and prevention of osteoarthritis. *PM & R: the journal of injury, function, and rehabilitation* 4 (5 Suppl), 59.

- Vincent, K. R., Conrad, B. P., Fregly, B. J. & Vincent, H. K. 2012. The pathophysiology of osteoarthritis: a mechanical perspective on the knee joint. *PM & R: the journal of injury, function, and rehabilitation* 4 (5 Suppl), 3.
- Vos, T., Flaxman, A. & Naghavi, M. 2012. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *LANCET* 380 (9859).
- Walker, C. R., Myles, C., Nutton, R. & Rowe, P. 2001. Movement of the knee in osteoarthritis. The use of electrogoniometry to assess function. *The Journal of bone and joint surgery. British volume* 83 (2), 195.
- Waller, B., Munukka, M., Rantalainen, T., Lammentausta, E., Nieminen, M. T., et al. 2017. Effects of high intensity resistance aquatic training on body composition and walking speed in women with mild knee osteoarthritis: a 4-month RCT with 12-month follow-up. *Osteoarthritis and Cartilage* 25 (8), 1238-1246.
- Waller, B., Ogonowska-Slodownik, A., Vitor, M., Lambeck, J., Daly, D., et al. 2014. Effect of therapeutic aquatic exercise on symptoms and function associated with lower limb osteoarthritis: systematic review with meta-analysis. *Physical therapy* 94 (10), 1383-1395.
- Wang, Y., Wei, L., Zeng, L., He, D. & Wei, X. 2013. Nutrition and degeneration of articular cartilage. *Knee Surgery, Sports Traumatology, Arthroscopy* 21 (8), 1751-1762.
- Ware, J. E. & Kosinski, M. 2001. Interpreting SF&36 summary health measures: A response. *Quality of life research* 10 (5), 405-413.
- Wieland, H. A., Michaelis, M., Rudolphi, K. A. & Kirschbaum, B. J. 2005. Osteoarthritis - an untreatable disease? *Nature Reviews Drug Discovery* 4 (4), 331-344.
- Wijayaratne, S. P., Teichtahl, A. J., Wluka, A. E., Hanna, F., Bell, R., et al. 2008. The determinants of change in patella cartilage volume-a cohort study of healthy middle-aged women. *Rheumatology* 47 (9), 1426-1429.
- Zacharias, A., Green, R. A., Semciw, A. I., Kingsley, M. I. C. & Pizzari, T. 2014. Efficacy of rehabilitation programs for improving muscle strength in people with hip or knee osteoarthritis: a systematic review with meta-analysis. *Osteoarthritis and Cartilage* 22 (11), 1752-1773.
- Zhang, W., Moskowitz, R. W., Nuki, G., Abramson, S., Altman, R. D., et al. 2008. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis and cartilage* 16 (2), 137-162.
- Zhang, Y. & Jordan, J. M. 2010. Epidemiology of Osteoarthritis. *Clinics in Geriatric Medicine* 26 (3), 355-369.



ORIGINAL PUBLICATIONS

I

EFFICACY OF A PROGRESSIVE AQUATIC RESISTANCE TRAINING FOR TIBIOFEMORAL CARTILAGE IN POSTMENOPAUSAL WOMEN WITH MILD KNEE OSTEOARTHRITIS: A RANDOMISED CONTROLLED TRIAL

by

Munukka M, Waller B, Rantalainen T, Häkkinen A, Nieminen M.T, Lammentausta E, Kujala U.M, Paloneva J, Sipilä S, Peuna A, Kautiainen H, Selänne H, Kiviranta I & Heinonen A. 2016

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Osteoarthritis and Cartilage



Efficacy of progressive aquatic resistance training for tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis: a randomised controlled trial



M. Munukka ^{† * a}, B. Waller ^{† ** a}, T. Rantalainen [‡], A. Häkkinen ^{† §}, M.T. Nieminen ^{|| ¶ #}, E. Lammentausta ^{||}, U.M. Kujala [†], J. Paloneva ^{††}, S. Sipilä ^{† ‡‡}, A. Peuna ^{|| ¶}, H. Kautiainen ^{§§ ||||}, H. Selänne ^{¶¶}, I. Kiviranta ^{###}, A. Heinonen [†]

[†] Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland

[‡] Institute for Physical Activity and Nutrition (IPAN), School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia

[§] Department of Physical Medicine and Rehabilitation, Central Finland Central Hospital, Jyväskylä, Finland

^{||} Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland

[¶] Research Unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland

[#] Medical Research Center, University of Oulu and Oulu University Hospital

^{††} Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland

^{‡‡} Gerontology Research Center, University of Jyväskylä, Finland

^{§§} Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland

^{||||} Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland

^{¶¶} Mehiläinen Sports Medical Clinic, Jyväskylä, Finland

^{###} Department of Orthopaedics and Traumatology, University of Helsinki, and Helsinki University Hospital, Helsinki, Finland

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SUMMARY

Objective: To study the efficacy of aquatic resistance training on biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis (OA).

Design: Eighty seven volunteer postmenopausal women, aged 60–68 years, with mild knee OA (Kellgren–Lawrence grades I/II and knee pain) were recruited and randomly assigned to an intervention ($n = 43$) and control ($n = 44$) group. The intervention group participated in 48 supervised aquatic resistance training sessions over 16 weeks while the control group maintained usual level of physical activity. The biochemical composition of the medial and lateral tibiofemoral cartilage was estimated using single-slice transverse relaxation time (T2) mapping and delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC index). Secondary outcomes were cardiorespiratory fitness, isometric knee extension and flexion force and knee injury and OA outcome (KOOS) questionnaire.

Results: After 4-months aquatic training, there was a significant decrease in both T2 -1.2 ms (95% confidence interval (CI): -2.3 to -0.1 , $P = 0.021$) and dGEMRIC index -23 ms (-43 to -3 , $P = 0.016$) in the training group compared to controls in the full thickness posterior region of interest (ROI) of the medial femoral cartilage. Cardiorespiratory fitness significantly improved in the intervention group by 9.8% ($P = 0.010$).

* Address correspondence and reprint requests to: M. Munukka, University of Jyväskylä, Department of Health Sciences, P.O. Box 35, FI-40014 University of Jyväskylä, Finland. Tel: 358-408053606, 358-408053569.

** Address correspondence and reprint requests to: B. Waller, University of Jyväskylä, Department of Health Sciences, P.O. Box 35, FI-40014 University of Jyväskylä, Finland. Tel: 358-408053606, 358-408053569.

E-mail addresses: matti.munukka@jyu.fi (M. Munukka), ben.waller@jyu.fi (B. Waller), t.rantalainen@deakin.edu.au (T. Rantalainen), arja.h.hakkinen@jyu.fi (A. Häkkinen), miika.nieminen@oulu.fi (M.T. Nieminen), eveliina.lammentausta@oulu.fi (E. Lammentausta), urho.m.kujala@jyu.fi (U.M. Kujala), juha.paloneva@ksshp.fi (J. Paloneva), sarianna.sipila@jyu.fi (S. Sipilä), arttu.peuna@ppshp.fi (A. Peuna), hannu.kautiainen@medcare.fi (H. Kautiainen), Harri.Selanne@likes.fi (H. Selänne), ilkka.kiviranta@helsinki.fi (I. Kiviranta), ari.o.heinonen@jyu.fi (A. Heinonen).

^a Both authors have equal contribution.

Conclusions: Our results suggest that, in postmenopausal women with mild knee OA, the integrity of the collagen-interstitial water environment (T2) of the tibiofemoral cartilage may be responsive to low shear and compressive forces during aquatic resistance training. More research is required to understand the exact nature of acute responses in dGEMRIC index to this type of loading. Further, aquatic resistance training improves cardiorespiratory fitness.

Trial registration number: ISRCTN65346593.

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Introduction

Knee osteoarthritis (OA) is a common cause of pain and limitations in physical function globally and represents a significant burden on healthcare costs¹. The development of knee OA progresses slowly over years². In the early phase of OA development, changes are seen in the biochemical composition of the cellular matrix of the cartilage. These include a decrease in glycosaminoglycan (GAG) content, responsible for hydrophilic properties of the collagen matrix, and loss of integrity of the collagen matrix, responsible for restraining hydrostatic pressure and maintaining cartilage stiffness³. As cartilage degeneration progresses its biomechanical properties are altered, reducing its ability to resist and distribute tensile, shear and compressive forces, causing further degradation and joint failure⁴.

There is no known cure or treatment that prevents or reverses the biochemical changes in the cartilage, therefore, the current management of OA focuses on reducing the symptoms and decreased function associated with the disease¹. Exercise, irrespective of modality (land or water) or type (strength or aerobic), has been shown to be effective in achieving these aims^{5,6}. Moreover, an active life style with participation in exercise has been shown to be beneficial for maintenance of the biochemical properties of cartilage in both animals^{7,8} and humans^{9,10}. Further, exercise has been shown to reverse cartilage atrophy seen in disuse and immobilisation studies^{11,12} and slow down progression of OA in animals¹³. Therefore, exercise could be an effective intervention for the maintenance of cartilage health. However, studies investigating the effect of exercise interventions on healthy and degenerated human cartilage are sparse^{14–17}. Only two previous studies have investigated the effects of land based exercise on the biochemical composition of cartilage in postmenopausal women with mild knee OA, i.e., Kellgren–Lawrence grades I/II and knee pain^{15,16}. We found an improvement in the collagen matrix in the patella cartilage of women with mild knee OA following a 1-year, three times a week, high-impact exercise intervention¹⁵ while we did not see any worsening or improvement in the collagen matrix or GAG concentration of the tibiofemoral cartilage in the same study¹⁶. Therefore, there is sufficient evidence to show cartilage health is maintained by appropriate mechanical stimulus and environment^{9,18}.

Pain is a major modulator for activity avoidance in people with knee OA¹⁹. Water is a facilitating environment in which persons with lower limb OA can safely and comfortably exercise at high intensities utilising full joint range of motions²⁰. Our recent systematic review showed that aquatic exercise has a similar effect on pain and self-reported functioning compared to land-based training⁶. Moreover, in our previous studies Pöyhönen *et al.*²¹ and Valtonen *et al.*²² both showed significant benefits of a progressive aquatic resistance training program for physical functioning in healthy women and following knee arthroplasty, respectively. Regular cyclic movements performed during aquatic exercise may provide sufficient mechanical stimulus and facilitate improved exchange of nutrients thus increasing chondrocyte activity^{4,18}. Therefore, the aim of this study was to investigate if progressive,

intensive and high volume aquatic resistance training affects the biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee OA.

Materials and methods

Study design

This study was a 4-month registered randomised controlled trial (ISRCTN65346593) with two experimental arms: (1) aquatic resistance training and (2) control. Recruitment and data collection took place between January 2012 and May 2013 and followed the published protocol without changes²³. Included participants were women aged 60–68 years with mild knee OA. In this study we classify mild knee OA as radiographic changes in tibiofemoral joint grades I (possible osteophytes) or II (definite osteophytes, possible joint space narrowing) according to the Kellgren–Lawrence (K/L) classification and experiencing knee pain on most days²⁴. The study protocol (Dnro 19U/2011) was approved by the Ethics Committee of the Central Finland Health Care District and conforms to the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Subject recruitment

A multistage recruitment process was implemented (Fig. 1). Initially, postmenopausal women from the Jyväskylä region in Central Finland were voluntarily recruited through advertisements in local newspapers. Preliminary eligibility was assessed using a structured telephone interview ($n = 323$), followed by evaluation of OA severity in the tibiofemoral joint with radiographs ($n = 180$) and finally through medical screening ($n = 111$). Inclusion criteria were: postmenopausal woman aged 60–68 years, experiencing knee pain on most days, participates in intensive exercise \leq twice a week, radiographic changes in tibiofemoral joint K/L I or II, no previous cancer or chemotherapy, no medical contraindications or other limitations to full participation in an intensive aquatic training program and complete transverse relaxation time (T2) data. Exclusion criteria included a T-score < -2.5 (indicating osteoporosis)²⁵ measured from the femoral neck using dual-energy X-ray absorptiometry (DXA), resting knee pain visual analogue scale (VAS) $> 50/100$, surgery of the knee due to trauma or knee instability, meniscectomy within the last 12 months, inflammatory joint disease, intra-articular steroid injections in the knee during the previous 12 months, contraindications to MRI and allergies to contrast agents or renal insufficiency. Due to confounding factors related to obesity, a body mass index (BMI) of $> 34 \text{ kg/m}^2$ was an exclusion criterion.

Randomisation and blinding

After baseline measurements, all participants were randomly allocated with a three digit identification number (ID) to blind

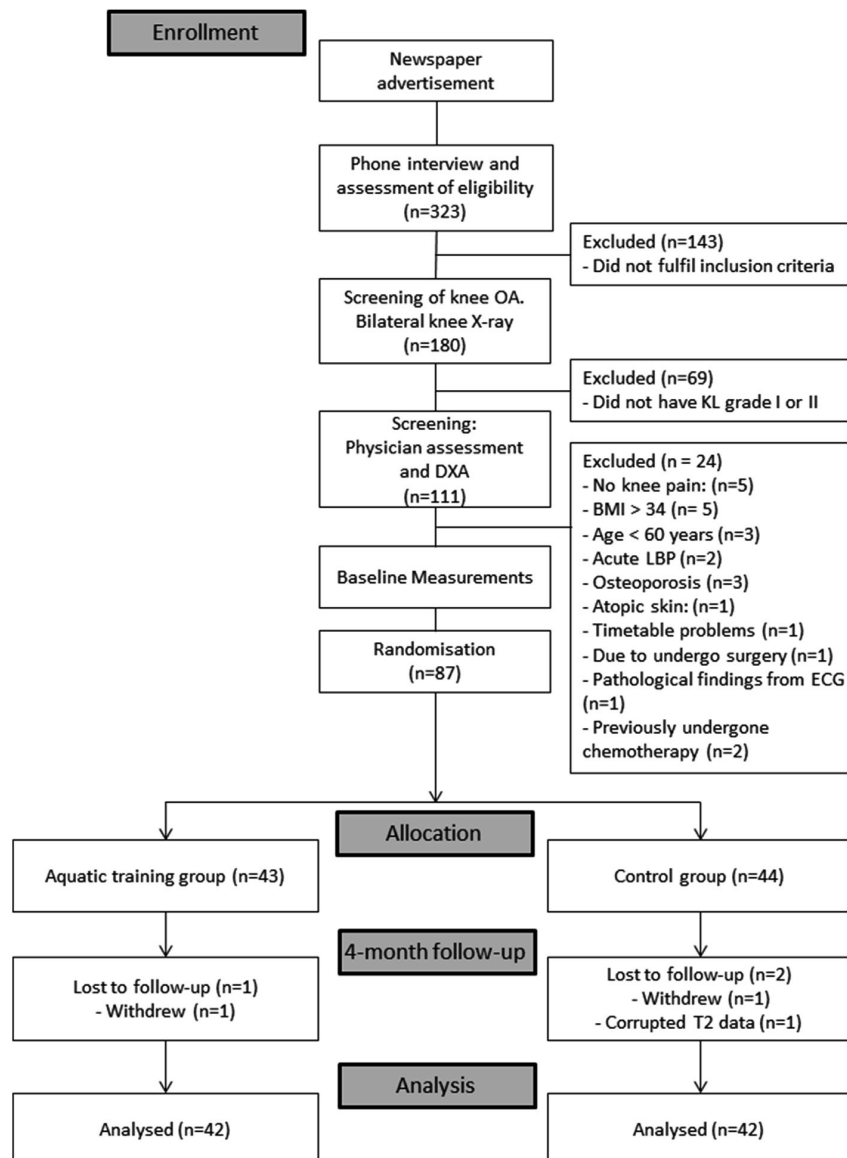


Fig. 1. Flow chart showing enrolment, allocation and 4 month end measurements.

researchers to intervention allocation and provision. A blinded statistician, only provided with ID and K/L grade, performed a computer generated block randomisation of size of 10, stratified according to K/L grade I or II. The MRIs were performed by external radiographers and segmentation was performed blinded to intervention allocation.

Health questionnaire

At baseline, a researcher-designed questionnaire was used to record physical activity levels, general health, medical conditions, current medications, menopausal status and hormone therapy. Leisure time physical activity levels, i.e., activity type (e.g., walking or golf), duration and intensity, prior to the study inclusion were converted into metabolic equivalent task (MET)-hours per week²⁶.

Primary outcome measures

Primary outcomes for this study were T2 relaxation time (T2 mapping (milliseconds, ms) and delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC index, ms). Images were taken using a Siemens Magnetom Symphony Quantum 1.5-T scanner (Siemens AG, Medical Solutions, Erlangen, Germany). Single sagittal slice images from the centre of the medial and lateral femoral condyles were taken from the knee with the highest K/L grade (affected knee). In cases of identical grading bilaterally, the right knee was imaged. Images were manually segmented using an in-house MATLAB application with built-in motion correction for dGEMRIC (Mathworks, Inc. Natick, MA, USA). In this study we divided the femoral cartilage into three region of interests (ROIs); anterior, central and posterior (Fig. 2). dGEMRIC indices were corrected for BMI²⁷. Precision, scan-rescan,

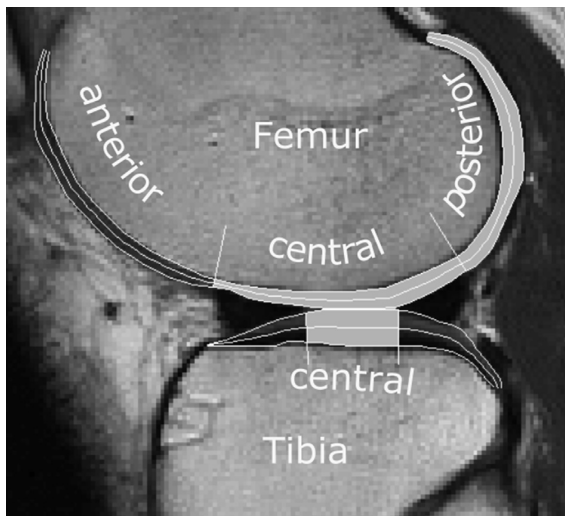


Fig. 2. Illustration of the ROIs in the full-thickness femoral and tibial cartilage. Midlines split both femoral and tibial cartilage into superficial and deep sections.

(CV_{RMS}) of dGEMRIC in asymptomatic subjects is 7% for full-thickness ROIs and 5% for bulk cartilage²⁸. In our laboratory, the inter-observer error (CV_{RMS}) for T2 full-thickness ROIs was 1.3–3.3% and 2.8–4.0% for dGEMRIC index. The full MRI protocol and example images are provided in the online supplemental material.

Secondary outcomes

Cardiorespiratory fitness (VO_2 peak, ml/kg/min) was estimated using the UKK 2 km walking test (UKK Institute, Tampere, Finland)²⁹. Isometric knee extension and flexion force (N) of the affected knee was measured using an adjustable dynamometer chair (Good strength; Metitur Ltd, Jyväskylä, Finland)³⁰.

Self-assessed impact of OA on pain, other symptoms, activities of daily living (ADL), sports and recreation (Sport) and knee related quality of life (QOL) were assessed using the validated Finnish³¹ Likert version of the knee injury and osteoarthritis outcome score (KOOS) questionnaire³². Scores for each domain range between 0 and 100, with a score of 0 indicating extreme and 100 no knee problems.

Daily physical activity

Daily physical activity, for the whole intervention period, of each participant was recorded using a leisure time physical activity diary from which metabolic equivalent task (MET-hours) per week was calculated²⁶. In week 13 of the intervention period the daily physical activity (excluding intervention) was measured for 3 consecutive days including one weekend day using an accelerometer (Hookie AM 20, Traxmeet Finland). Mean amplitude deviation (MAD) of the resultant acceleration signal for each 5-s epoch were calculated and categorized according to Vähä-Ypyä *et al.*³³.

Exercise protocol

The participants in the intervention group received 1 h of supervised lower limb aquatic resistance training three times a week for 16 weeks, for a total of 48 training sessions. Resistance of exercises was progressed with three different levels: barefoot, small fins and large resistance boots²¹ and the training leg performed all the movements without contact with the pool walls or bottom i.e., non-weight bearing. The intervention was completed in small

groups of 6–8 subjects in a pool heated to 30–32° with two instructors: one ensuring intensity and the other full range of movement. Intensity of the training sessions was set at “as hard and fast as possible” to ensure maximal muscle contraction. Pöyhönen *et al.*³⁴ discovered that during maximal knee flexion and extension exercises in water with large resistance boots the drag forces produced were 80–85% (145 ± 30 N) of maximal isokinetic movements. Full range of motion was strictly controlled for to ensure optimal movement of synovial fluid and exposure of the whole cartilage to the low compressive and shear forces created by the muscle contraction and movement. Training intensity was monitored using heart rate monitors (Polar Electro Ltd, Kempele, Finland), rate of perceived exertion (RPE) using the Borg 6–20 scale³⁵ and number of repetitions achieved per movement. Full description of exercises and training methodology can be found from the online supplemental material.

Control group

The control group maintained usual care and were asked to continue their usual leisure time activities. They were offered the possibility of participating in two sessions consisting of 1 h of light stretching and relaxation during the 4-month intervention period.

Statistical analyses

The main outcome variables were analysed according to the intention-to-treat analysis principle. Changes in all outcomes were analysed using the bootstrap type analysis of covariance (ANCOVA); confidence interval (CI) were obtained by bias-corrected bootstrapping (5000 replications) due to violation of distributions assumptions. T2 was adjusted for baseline value, height and weight and dGEMRIC index was adjusted for baseline value only. Secondary outcomes were adjusted for baseline value. There are multiple endpoints in this study, and results have to be viewed with certain provisos. All *P*-values and CIs are quoted, rather than introducing the problems and potential errors associated with formal adjustments for potential multiplicity issues. Between-group changes in all outcomes are reported in text as mean difference (95% CI, adjusted *P*-value). Effect size (*d*) was calculated by using the method of Cohen³⁶ where an effect size of 0.20 is considered small, 0.50 moderate, and 0.80 large. CIs for the effect sizes were obtained by bias-corrected bootstrapping (5000 replications). Statistical analyses were performed using statistical software (Stata, release 13.1, StataCorp, College Station, Texas).

Target sample size of 70 (35 per research arm) was required to ensure the power of at least 80% to detect a difference of 40 ms effect in dGEMRIC between the groups at two-side $\alpha = 0.05$. Predicting a dropout rate of about 10% we aimed to recruit at least 90 participants at baseline.

Results

In total 87 participants met the inclusion criteria and were randomised into the aquatic training group ($n = 43$) and control group ($n = 44$) (Fig. 1). The demographic and clinical characteristics of both groups were similar at baseline (Table 1).

Program feasibility

Drop-out rate, during the 4-month intervention period, for each group was 2.3% ($n = 1$ per group) (Fig. 1). Training compliance was 88% and mean (SD) training frequency was 2.6 (0.5) times per week (including dropouts). The average intensity of each training session was RPE 15 (range, 12–17) and average (SD) maximum heart rate was 144 (12) beats per minute. The mean (SD) number of repetitions completed per session with the affected leg was 481 (67), 416

Table I
Baseline demographic and clinical characteristics of the participants

	Exercise group (n = 43)	Control group (n = 44)
Age (years)	64 (2)	64 (2)
Height (cm)	162 (5)	162 (5)
Body mass (kg)	69.6 (10.3)	71.0 (11.3)
Body mass index (kg/m ²)	26.6 (3.8)	27.1 (3.5)
Time from menopause (years)	14 (6)	14 (6)
Pain killers for knee pain, n (%) of users	11 (25.6)	9 (20.5)
Glucosamine use occasionally, n (%)	12 (28)	8 (18)
Kellgren–Lawrence grade, n (%)		
Grade 1	23 (53.5)	24 (54.5)
Grade 2	20 (46.5)	20 (45.5)
Knee pain during last week, (VAS, mm)*		
• Affected leg	28 (25)	24 (19)
• Non-affected leg	24 (19)	23 (18)
Habitual physical activity (METH/week)	29 (31)	36 (33)

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

* Range, 0–100 mm.

(68) and 387 (58) for barefoot, small fins and large boots, respectively. 70.5% of these repetitions involved full knee active extension and flexion which was mean 134.4 (SD, 5.6) degrees (affected knee) as measured during baseline assessment.

Harms

There were two medical consultations (bilateral knee pain and dyspnoea) as a result of the aquatic training. One subject from the control group required a medical consultation for knee pain after the baseline physical performance measures. All three subjects continued their participation in the study and attended follow-up measurements.

Primary outcomes

To ensure accuracy, each MRI image was inspected for quality. One participant was excluded from the study due to corrupted data as a result of excessive movement artefact in T2 images (Fig. 1). One complete baseline dGEMRIC index data set was missing due to lost images (at time of imaging). Additionally, from the dGEMRIC index 11 medial compartments had movement artefact, while in the lateral compartment, 14 had artery-flow pulsating artefact, one had movement artefact and one inaccurate location of the slice compared to baseline image. In total 72 and 68 complete dGEMRIC data sets for medial and lateral femoral condyles respectively were available for quantitative analysis.

Table II
Effects of aquatic training on T2 relaxation time and dGEMRIC index in full-thickness ROIs

	Baseline, mean (SD)		Change to month 4, mean (95% CI)		Effect size (95% CI)	P-value	
	Training (n = 42)	Controls (n = 42)	Training (n = 42)	Controls (n = 42)		Crude	Adjusted
T2, ms							
Femur							
Lateral condyle							
Central	52.6 (4.9)	53.4 (4.1)	-0.18 (-1.05 to 0.59)	-0.03 (-0.95 to 0.91)	0.05 (-0.38 to 0.48)	0.81	0.58‡
Posterior	49.6 (4.6)	48.8 (3.6)	-0.23 (-1.26 to 0.97)	0.74 (0.01 to 1.40)	0.31 (-0.12 to 0.74)	0.15	0.30‡
Medial condyle							
Central	52.8 (4.5)	52.0 (4.4)	-0.20 (-1.17 to 0.83)	0.48 (-0.71 to 1.68)	0.18 (-0.25 to 0.61)	0.40	0.47‡
Posterior	52.0 (4.7)	51.9 (4.5)	-1.16 (-1.85 to -0.50)	0.10 (-0.72 to 0.94)	0.48 (0.05 to 0.91)	0.028	0.021‡
Tibia							
Lateral plateau							
Central	41.0 (8.3)	42.9 (8.1)	-0.66 (-1.86 to 0.45)	0.05 (-1.67 to 1.68)	0.15 (-0.28 to 0.58)	0.50	0.30‡
Medial plateau							
Central	44.5 (5.0)	42.7 (4.2)	-0.02 (-1.45 to 1.41)	-0.02 (-0.85 to 0.79)	-0.00 (-0.43 to 0.43)	1.00	0.41‡
dGEMRIC*, ms							
Femur							
Lateral condyle⁺							
Central	433 (70)	424 (44)	-4 (-16 to 7)	-1 (-11 to 8)	0.07 (-0.40 to 0.55)	0.77	0.93‡
Posterior	422 (60)	428 (57)	2 (-10 to 16)	6 (-8 to 22)	0.08 (-0.40 to 0.57)	0.72	0.71‡
Medial condyle[§]							
Central	411 (61)	410 (65)	-19 (-32 to -6)	-6 (-17 to 7)	0.34 (-0.12 to 0.80)	0.14	0.13‡
Posterior	453 (60)	448 (61)	-23 (-39 to -8)	1 (-14 to 16)	0.53 (0.06 to 0.99)	0.022	0.022‡
Tibia							
Lateral plateau							
Central	424 (76)	419 (82)	-1 (-20 to 17)	1 (-15 to 17)	0.03 (-0.46 to 0.52)	0.91	0.95‡
Medial plateau							
Central	382 (75)	386 (50)	-20 (-35 to -6)	-6 (-20 to 8)	0.32 (-0.15 to 0.78)	0.19	0.09‡

In T2 low values correspond to improved integrity and orientation of the collagen fibres and a decrease in hydration of articular cartilage. In dGEMRIC, high values correspond to high GAG concentration.

* Missing data for dGEMRIC ⁺n = 16, [§]n = 12.

‡ ANCOVA: adjusted for baseline value, height and weight.

‡ ANCOVA: adjusted for baseline value.

T2 and dGEMRIC index baseline values, changes, group differences and effect sizes (Cohen's *d*) at the end of the 4-month intervention are given in Table II. There was a significant decrease in both T2, mean difference -1.2 ms (95% CI: -2.2 to -0.2 , $P = 0.021$) and dGEMRIC index -23 ms (-43 to -3 , $P = 0.022$) in the training group compared to controls in the full thickness posterior ROI of the medial femoral cartilage. Further, significant decreases in the training group compared to controls were only seen in the deep posterior and not superficial ROI of the medial femoral cartilage, -1.6 ms (-3.0 to -0.3 , $P = 0.016$), and -26 ms (-50 to -3 , $P = 0.030$), for T2 and dGEMRIC index respectively (Fig. 3). Values for the deep and superficial posterior ROI (Fig. 3) can be found from the online supplemental material.

Secondary outcomes

Cardiorespiratory fitness VO_2 peak increased 9.8% in the training group and 4.4% in the control group ($d = 0.58$, $P = 0.010$). There were no between group differences in the knee extension or flexion muscle force or in any domains of KOOS (Table III).

Daily physical activity

The total mean (SD) MET-hours per week, including the intervention, were 40 (13) and 26 (16) in the training and control group respectively ($P < 0.001$). No between group differences were seen in MET activity once the intervention activity was removed ($P = 0.112$). There was no significant difference between the groups in physical activity as measured with accelerometers, excluding the

intervention. Sedentary behaviour accounted for 80% (5.0) or 13,903 (869) MADs of daily activity. The remaining physical activity was divided into slow walking 3166 (821), normal walking 198 (175) and brisk walking jogging and running together 1.7 (1.4) MADs.

Discussion

As far as we know, this is the first study to show a response in the biochemical composition of tibiofemoral cartilage following 4-months of progressive aquatic resistance training in postmenopausal women with mild knee OA. A small significant change was observed in the biochemical composition of the medial posterior femoral cartilage, which is less loaded during ADL³⁷. Additionally, the training significantly improved cardiorespiratory capacity but had no significant effect on muscle force and self-reported symptoms.

This is the first study to show concurrent changes in both T2 and dGEMRIC index in an exercise intervention study. However, both MRI techniques have only been previously implemented once in the same study. In the study by Multanen *et al.*¹⁶ we investigated the effects of a land-based impact intervention on the biochemical composition tibiofemoral cartilage in postmenopausal women with mild knee OA. No positive or negative effect was observed with either MRI technique, however, the posterior ROIs were not reported. In this previous study¹⁶ the degree of knee motion during the land-based intervention was 0–65° and therefore the posterior ROI was not directly loaded. Knee flexion of over 90° is required to produce contact between the posterior ROI of the femur and central tibia³⁸ which was achieved with our intervention at high frequency. Therefore, our results suggest that the chondrocytes in the posterior region of the femoral cartilage in persons with mild knee OA may have a lower threshold for adaption compared to the central and might be more responsive to the high repetition low shear and compressive cyclic forces produced in the aquatic resistance training. In contrast, the chondrocytes in the central region of the femur and tibia cartilage may require a higher or atypical load to stimulate an adaptive response. Further, the response was limited to the medial femoral cartilage possibly due to anatomical differences. The medial tibial plateau is concave compared to the convex surface of the lateral side, thus on the medial tibiofemoral joint there is greater contact between the cartilage surfaces³⁹.

After 4-months of aquatic resistance training, T2 in the posterior region of the medial femoral condyle significantly decreased, with no change in the central femur and tibia regions. A decrease in T2 values is indicative of improved integrity and orientation of the collagen fibres and a decrease in hydration of articular cartilage^{40,41}. In more detailed analysis we found that decrease in T2 occurred in deep posterior region of medial femoral cartilage which is in line with our previous study¹⁵. This study¹⁵ showed a similar response in T2 in patella cartilage in women with mild knee OA following a 1 year intervention. While the intervention was different, the mechanical forces in the patella cartilage during the progressive impact exercises were shear with moderate compression in the patellofemoral joint i.e., forces were not directly compressive as in the tibiofemoral joint¹⁶. Therefore, our findings support the notion that the collagen-interstitial water environment in the tibiofemoral cartilage may respond to exercise.

We found a corresponding significant decrease in dGEMRIC index in the posterior region of medial femoral cartilage and again more specifically in its deep region. A lower dGEMRIC index is associated with a lower GAG concentration, thus, a decrease in dGEMRIC index may indicate degeneration of cartilage^{42,43}. Our results suggest that the aquatic resistance training may have produced a decrease in GAG concentration within the cartilage matrix

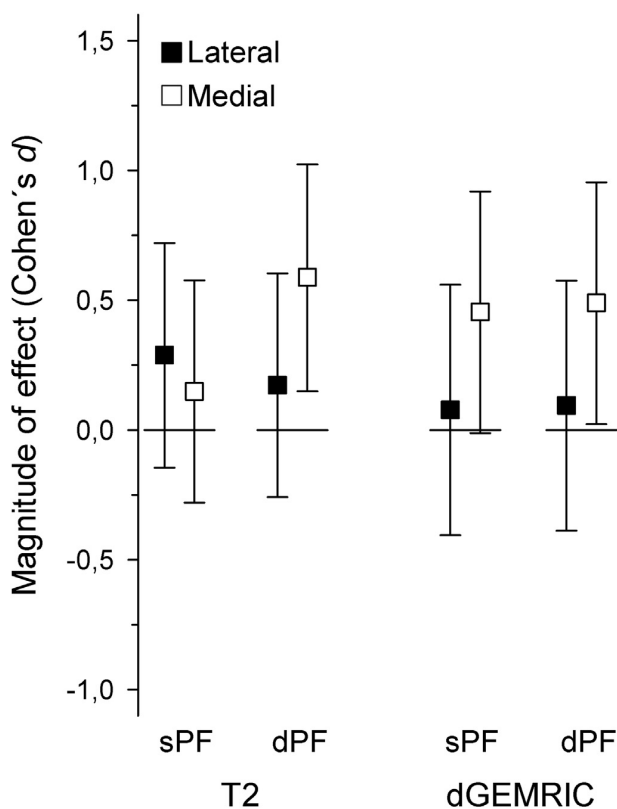


Fig. 3. Magnitude of effect (Cohen's *d* and 95% CI) at superficial and deep layers of T2 and dGEMRIC cartilage ROIs from medial and lateral condyles. sPF = superficial posterior femur; dPF = deep posterior femur.

Table III
Effects of aquatic training on physical performance and clinical symptoms

	Baseline, mean (SD)		Change to month 4, mean (95% CI)		Effect size (95% CI)	P-value	
	Training (n = 42)	Controls (n = 42)	Training (n = 42)	Controls (n = 42)		Crude	Adjusted*
Cardiorespiratory fitness (ml/kg/min)							
Estimated VO ₂ peak	24.6 (5.6)	24.9 (4.9)	2.4 (1.8 to 3.1)	1.1 (0.5 to 1.8)	0.58 (0.15 to 1.06)	0.006	0.010
Force (N)							
Extension	335 (64)	343 (70)	20 (8 to 33)	9 (–5 to 23)	0.27 (–0.17 to 0.70)	0.22	0.28
Flexion	164 (52)	165 (40)	20 (9 to 30)	17 (7 to 27)	0.07 (–0.36 to 0.51)	0.74	0.71
KOOS (0–100)							
Pain	80 (10)	82 (12)	4 (1 to 7)	1 (–2 to 4)	0.30 (–0.14 to 0.74)	0.17	0.25
Other symptoms	74 (13)	75 (14)	7 (3 to 10)	2 (–1 to 6)	0.37 (–0.07 to 0.81)	0.09	0.09
ADL	84 (10)	85 (11)	4 (1 to 7)	0 (–2 to 3)	0.39 (–0.03 to 0.78)	0.08	0.10
Sport	63 (20)	65 (22)	8 (2 to 14)	3 (–3 to 8)	0.27 (–0.16 to 0.73)	0.21	0.24
QOL	65 (17)	71 (20)	7 (3 to 11)	3 (–1 to 8)	0.26 (–0.18 to 0.71)	0.24	0.38

* ANCOVA: adjusted for baseline.

or faster contrast agent diffusion in to the cartilage through increased permeability of the cartilage surface⁴⁴, which are characteristics of OA progression⁴. These results conflict with the findings of Roos and Dahlberg¹⁴ who found an increase in the T1 relaxation time in the presence of contrast agent following a 4-month neuromuscular training intervention. However, they measured only one ROI from the medial femoral cartilage and dGEMRIC values were not corrected for BMI, also their population was younger people at high risk of developing knee OA following surgery for meniscal injury. Alternatively, in a previous cross sectional study⁴⁵, similar associations i.e., lower T2 and dGEMRIC index was seen in the central ROI of the patella cartilage in young people with repetitive patella dislocation⁴⁵. This finding was speculated to be due to a reparative process within the cartilage. Additionally, faster diffusion of the contrast agent into the medial tibiofemoral cartilage after intravenous injection may have been a combined result of improved contrast agent delivery through vascular changes i.e., increased blood flow in the subchondral bone and synovium with possible improvements in lower limb biomechanics. Further, an improved diffusion of the contrast agent could be explained by a decrease in cartilage thickness i.e., reversal of the cartilage swelling characterised in early OA^{4,46}. Cartilage thickness was not measured in our study leaving this issue to speculation and open for further investigation in the future. Therefore, we could hypothesise that while our results indicate the integrity of the collagen-interstitial water environment may be responsive to shear/compressive forces during aquatic exercise, further research is required to understand the exact nature of acute responses in dGEMRIC index to this type of loading.

In line with the findings of our recent systematic review⁶, we did not see a significant change in muscle force. However, we used isometric muscle testing whereas, the muscle contraction during isokinetic strength testing mimics closer the true muscle work performed during aquatic resistance training and could have been more sensitive to change. The improvements in cardiorespiratory fitness are in line with other studies investigating the effects of aquatic training⁴⁷. An aquatic exercise program which also includes neuromuscular exercises e.g., partial weight bearing exercises might produce better improvements in neuromuscular performance and possibly stimulate GAG production¹⁴ as it is possible to speculate that the loading mechanics in our study may have been ineffective for this purpose. There were no between group changes in any of the domains of the KOOS, this lack of significance is not a surprise given the high values reported at baseline. In combination with the results from the measures of physical performance and KOOS there is no indication that aquatic exercises had a harmful effect on clinical findings in this population. Therefore, aquatic resistance training of sufficient intensity to improve

cardiorespiratory function is well tolerated, has high compliance and does not increase pain in women with mild knee OA. Further research should focus on the efficacy of aquatic resistance training for people with more severe stages of OA progression.

The strengths of this study include the high adherence to a highly intensive aquatic training program. This study fulfilled all the important quality criteria of an RCT, except for blinding the participants to exercise therapy, which is common in exercise therapy studies⁴⁸. Strict imaging procedure and segmentation rules ensured good stability and repeatability of the T2 and dGEMRIC indices. This limits, but does not rule out, the possibility that the results of this study are affected by the magic angle (particularly T2) and partial volume effects. The long imaging time in dGEMRIC mapping might result in motion artefact which was controlled for in our study by using a motion correction technique built into the in-house software, as well as strict inclusion/exclusion criteria for image quality. Minor limitations include: MRI imaging performed with a 1.5 T scanner, whereas a 3.0 T scanner would have produced better spatial resolution and higher signal-to-noise ratio. The mean changes seen in T2 and dGEMRIC index fall within the upper limits of our measurement error for both techniques therefore we cannot exclude measurement error as a possible explanation for our findings. Further, this study had multiple endpoints and therefore results have to be viewed with caution. In some cases, occasionally thinned and deteriorated cartilage and movement or pulsating artery artefact prevented reliable segmentation of cartilage resulting in lost data. Also, we used single-slice segmenting method assessing articular cartilage, whereas multi-slice method might have produced a more comprehensive view of the knee cartilage. The MRI analysis application divided cartilage to deep and superficial compartments (50%/50%) and due to the 1.5T scanner used, segmented cartilage thickness was from two to five voxels reducing the spatial accuracy and therefore care should be taken when interpreting these results. Pre-contrast T1 imaging was not used in this study however its importance has been questioned and it is felt this omission does not affect our conclusions^{46,49}. Classification of OA severity was performed using a combination of pain and Kellgren–Lawrence classification (weight-bearing) and therefore it was not possible to differentiate between healthy and biomechanically altered cartilage between ROIs and condyles⁵⁰. It is still unknown if an aquatic training program of longer than 4-months would have created a global response throughout the cartilage. It is plausible to hypothesise that as cartilage health in one ROI improves it may cause a positive response in adjacent ROI's. Due to the strict inclusion criteria, our results cannot be directly applied to people with later stage OA, older or obese women and men. Finally, the authors acknowledge that the different qMRI parameters and their interactions are not yet fully understood and further investigations

about the interaction between exercise and these parameters are warranted.

Our results suggest that, in postmenopausal women with mild knee OA, the integrity of the collagen-interstitial water environment (T2) of the tibiofemoral cartilage may be responsive to low shear and compressive forces during aquatic resistance training. Further research is required to understand the exact nature of acute responses in dGEMRIC index to this type of loading. Clinical relevance of our findings remains unclear but strongly warrants further research. Additionally, aquatic resistance training of sufficient intensity to improve cardiorespiratory function is well tolerated, has high compliance and low risk of harm amongst women with mild knee OA.

Author contributions

Munukka, Matti: Analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding, collection and assembly of data.

Waller, Benjamin: Analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, obtaining of funding, collection and assembly of data.

Rantalainen, Timo: Analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support, collection and assembly of data.

Häkkinen, Arja: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

Nieminen, Miika: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support.

Lammentausta, Eveliina: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support.

Kujala, Urho: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article.

Paloneva, Juha: Analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Sipilä, Sarianna: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Peuna, Arttu: Analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, administrative, technical, or logistic support, collection and assembly of data.

Kautiainen, Hannu: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article for important intellectual content, final approval of the article, statistical expertise, collection and assembly of data.

Selänne, Harri: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Kiviranta, Ilkka: Conception and design, analysis and interpretation of the data, critical revision of the article for important intellectual content, final approval of the article.

Heinonen, Ari: Conception and design, analysis and interpretation of the data, drafting of the article, critical revision of the article

for important intellectual content, final approval of the article, obtaining of funding.

Conflict of interest

There is no conflict of interest for any authors.

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Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.joca.2016.05.007>.

References

- McAlindon T, Bannuru R, Sullivan M, Arden N, Berenbaum F, Bierma-Zeinstra S, *et al.* OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage* 2014;22:363–88.
- Roos EM, Arden NK. Strategies for the prevention of knee osteoarthritis. *Nat Rev Rheumatol* 2016;12:92–101, <http://dx.doi.org/10.1038/nrrheum.2015.135>.
- Goldring MB, Goldring SR. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Ann N Y Acad Sci* 2010;1192:230–7.
- Arokoski J, Jurvelin J, Väättäinen U, Helminen H. Normal and pathological adaptations of articular cartilage to joint loading. *Scand J Med Sci Sports* 2000;10:186–98.
- Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee. *Br J Sports Med* 2015;49:1554–7, <http://dx.doi.org/10.1002/14651858.CD004376.pub3>. 10.1136/bjsports-2015-095424.
- Waller B, Ogonowska-Slodownik A, Vitor M, Lambeck J, Daly D, Kujala UM, *et al.* Effect of therapeutic aquatic exercise on symptoms and function associated with lower limb osteoarthritis: systematic review with meta-analysis. *Phys Ther* 2014;94:1383–95, <http://dx.doi.org/10.2522/ptj.20130417>.
- Kiviranta I, Tammi M, Jurvelin J, Saamanen AM, Helminen HJ. Moderate running exercise augments glycosaminoglycans and thickness of articular cartilage in the knee joint of young beagle dogs. *J Orthop Res* 1988;6:188–95, <http://dx.doi.org/10.1002/jor.1100060205>.
- Kiviranta I, Tammi M, Jurvelin J, Arokoski J, Saamanen AM, Helminen HJ. Articular cartilage thickness and glycosaminoglycan distribution in the canine knee joint after strenuous running exercise. *Clin Orthop Relat Res* 1992;302–8.
- Teichtahl AJ, Wluka AE, Forbes A, Wang Y, English DR, Giles GG, *et al.* Longitudinal effect of vigorous physical activity on patella cartilage morphology in people without clinical knee disease. *Arthritis Rheum* 2009;61:1095–102.
- Tiderius CJ, Svensson J, Leander P, Ola T, Dahlberg L. dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) indicates adaptive capacity of human knee cartilage. *Magn Reson Med* 2004;51:286–90.
- Kiviranta I, Tammi M, Jurvelin J, Arokoski J, Säämänen A, Helminen HJ. Articular cartilage thickness and glycosaminoglycan distribution in the young canine knee joint after remobilization of the immobilized limb. *J Orthop Res* 1994;12:161–7.

12. Souza RB, Baum T, Wu S, Feeley BT, Kadel N, Li X, et al. Effects of unloading on knee articular cartilage T1rho and T2 magnetic resonance imaging relaxation times: a case series. *J Orthop Sports Phys Ther* 2012;42:511–20.
13. Brismar BH, Lei W, Hjerpe A, Svensson O. The effect of body mass and physical activity on the development of guinea pig osteoarthritis. *Acta Orthop Scand* 2003;74:442–8.
14. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis Rheum* 2005;52:3507–14, <http://dx.doi.org/10.1002/art.21415>.
15. Koli J, Multanen J, Kujala UM, Häkkinen A, Nieminen MT, Kautiainen H, et al. Effect of exercise on patellar cartilage in women with mild knee osteoarthritis. *Med Sci Sports Exerc* 2015;47:1767–74, <http://dx.doi.org/10.1249/MSS.0000000000000629>.
16. Multanen J, Nieminen MT, Häkkinen A, Kujala UM, Jämsä T, Kautiainen H, et al. Effects of high-impact training on bone and articular cartilage: 12-month randomized controlled quantitative MRI study. *J Bone Miner Res* 2014;29:192–201.
17. Hawezi ZK, Lammontausta E, Svensson J, Roos EM, Dahlberg LE, Tiderius CJ. Regional dGEMRIC analysis in patients at risk of osteoarthritis provides additional information about activity related changes in cartilage structure. *Acta Radiol* 2015;57:468–74, <http://dx.doi.org/10.1177/0284185115591237>.
18. Wang Y, Wei L, Zeng L, He D, Wei X. Nutrition and degeneration of articular cartilage. *Knee Surg Sports Traumatol Arthrosc* 2013;21:1751–62.
19. Holla JF, Sanchez-Ramirez DC, van der Leeden M, Ket JC, Roorda LD, Lems WF, et al. The avoidance model in knee and hip osteoarthritis: a systematic review of the evidence. *J Behav Med* 2014;37:1226–41.
20. Roper JA, Bressel E, Tillman MD. Acute aquatic treadmill exercise improves gait and pain in people with knee osteoarthritis. *Arch Phys Med Rehabil* 2013;94:419–25, <http://dx.doi.org/10.1016/j.apmr.2012.10.027>.
21. Pöyhönen T, Sipilä S, Keskinen KL, Hautala A, Savolainen J, Mäkiä E. Effects of aquatic resistance training on neuromuscular performance in healthy women. *Med Sci Sports Exerc* 2002;34:2103–9, <http://dx.doi.org/10.1249/01.MSS.0000039291.46836.86>.
22. Valtonen A, Pöyhönen T, Sipilä S, Heinonen A. Effects of aquatic resistance training on mobility limitation and lower-limb impairments after knee replacement. *Arch Phys Med Rehabil* 2010;91:833–9, <http://dx.doi.org/10.1016/j.apmr.2010.03.002>.
23. Waller B, Munukka M, Multanen J, Rantalainen T, Pöyhönen T, Nieminen MT, et al. Effects of a progressive aquatic resistance exercise program on the biochemical composition and morphology of cartilage in women with mild knee osteoarthritis: protocol for a randomised controlled trial. *BMC Musculoskelet Disord* 2013;14, <http://dx.doi.org/10.1186/1471-2474-14-82>.
24. Kellgren JH, Lawrence JS. Radiological assessment of osteoarthritis. *Ann Rheum Dis* 1957;16:494–502.
25. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ, Khaltaev N. A reference standard for the description of osteoporosis. *Bone* 2008;42:467–75.
26. Ainsworth BE, Haskell WL, Herrmann SD, Meckes N, Bassett Jr DR, Tudor-Locke C, et al. 2011 compendium of physical activities: a second update of codes and MET values. *Med Sci Sports Exerc* 2011;43:1575–81, <http://dx.doi.org/10.1249/MSS.0b013e31821ece12>.
27. Tiderius C, Hori M, Williams A, Sharma L, Prasad PV, Finnell M, et al. dGEMRIC as a function of BMI. *Osteoarthritis Cartilage* 2006;14:1091–7. S1063-4584(06)00154-3 [pii].
28. Multanen J, Rauvala E, Lammontausta E, Ojala R, Kiviranta I, Häkkinen A, et al. Reproducibility of imaging human knee cartilage by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5 Tesla. *Osteoarthritis Cartilage* 2009;17:559–64.
29. Laukkanen R, Oja R, Pasanen M, Vuori I. Criterion validity of a two-kilometer walking test for predicting the maximal oxygen uptake of moderately to highly active middle-aged adults. *Scand J Med Sci Sports* 1993;3:267–72.
30. Sipilä S, Multanen J, Kallinen M, Era P, Suominen H. Effects of strength and endurance training on isometric muscle strength and walking speed in elderly women. *Acta Physiol Scand* 1996;156:457–64, <http://dx.doi.org/10.1046/j.1365-201X.1996.461177000.x>.
31. Koli J, Multanen J, Häkkinen A, Kiviranta I, Kujala U, Heinonen A. Reliability of the Finnish versions of WOMAC and KOOS forms for knee osteoarthritis. *Physiotherapy* 2011;97:D203–4.
32. Roos EM, Roos H, Ekdahl C, Lohmander L. Knee injury and osteoarthritis outcome score (KOOS)-validation of a Swedish version. *Scand J Med Sci Sports* 1998;8:439–48.
33. Vähä-Ypyä H, Vasankari T, Husu P, Suni J, Sievänen H. A universal, accurate intensity-based classification of different physical activities using raw data of accelerometer. *Clin Physiol Funct Imaging* 2015;35:64–70.
34. Pöyhönen T, Keskinen KL, Kyröläinen H, Hautala A, Savolainen J, Mäkiä E. Neuromuscular function during therapeutic knee exercise under water and on dry land. *Arch Phys Med Rehabil* 2001;82:1446–52.
35. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14:377–81.
36. Faraone SV. Interpreting estimates of treatment effects: implications for managed care. *P T* 2008;33:700–11.
37. Walker CR, Myles C, Nutton R, Rowe P. Movement of the knee in osteoarthritis. The use of electrogoniometry to assess function. *J Bone Joint Surg Br* 2001;83:195–8.
38. Goyal K, Tashman S, Wang JH, Li K, Zhang X, Harner C. *In vivo* analysis of the isolated posterior cruciate ligament-deficient knee during functional activities. *Am J Sports Med* 2012;40:777–85, <http://dx.doi.org/10.1177/0363546511435783>.
39. Neumann DA. *Kinesiology of the Musculoskeletal System: Foundations for Physical Rehabilitation*. St. Louis: USA: Mosby; 2002:435–76.
40. Lammontausta E, Kiviranta P, Nissi M, Laasanen M, Kiviranta I, Nieminen M, et al. T2 relaxation time and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) of human patellar cartilage at 1.5 T and 9.4 T: relationships with tissue mechanical properties. *J Orthop Res* 2006;24:366–74.
41. Nieminen MT, Rieppo J, Töyräs J, Hakumäki JM, Silvennoinen J, Hyttinen MM, et al. T2 relaxation reveals spatial collagen architecture in articular cartilage: a comparative quantitative MRI and polarized light microscopic study. *Magn Reson Med* 2001;46:487–93.
42. Bashir A, Gray M, Hartke J, Burstein D. Nondestructive imaging of human cartilage glycosaminoglycan concentration by MRI. *Magn Reson Med* 1999;41:857–65.
43. Nissi M, Töyräs J, Laasanen M, Rieppo J, Saarakkala S, Lappalainen R, et al. Proteoglycan and collagen sensitive MRI evaluation of normal and degenerated articular cartilage. *J Orthop Res* 2004;22:557–64.
44. Li W, Scheidegger R, Wu Y, Edelman RR, Farley M, Krishnan N, et al. Delayed contrast-enhanced MRI of cartilage: comparison

- of nonionic and ionic contrast agents. *Magn Reson Med* 2010;64:1267–73.
45. Bengtsson Moström E, Lammentausta E, Finnbogason T, Weidenhielm L, Janarv P, Tiderius CJ. Pre-and postcontrast T1 and T2 mapping of patellar cartilage in young adults with recurrent patellar dislocation. *Magn Reson Med* 2014;74: 1363–9.
 46. Hawezi ZK, Lammentausta E, Svensson J, Dahlberg LE, Tiderius CJ. *In vivo* transport of Gd-DTPA2 – in human knee cartilage assessed by depth-wise dGEMRIC analysis. *J Magn Reson Imaging* 2011;34:1352–8.
 47. Lim J, Tchai E, Jang S. Effectiveness of aquatic exercise for obese patients with knee osteoarthritis: a randomized controlled trial. *PM R* 2010;2:723–31.
 48. Furlan AD, Pennick V, Bombardier C, van Tulder M, Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine* 2009;34:1929–41, <http://dx.doi.org/10.1097/BRS.0b013e3181b1c99f>.
 49. Li W, Du H, Scheidegger R, Wu Y, Prasad PV. Value of pre-contrast T(1) for dGEMRIC of native articular cartilage. *J Magn Reson Imaging* 2009;29:494–7, <http://dx.doi.org/10.1002/jmri.21658>.
 50. Multanen J, Heinonen A, Hakkinen A, Kautiainen H, Kujala UM, Lammentausta E, et al. Bone and cartilage characteristics in postmenopausal women with mild knee radiographic osteoarthritis and those without radiographic osteoarthritis. *J Musculoskelet Neuronal Interact* 2015;15:69–77.



II

EFFECTS OF PROGRESSIVE AQUATIC RESISTANCE TRAINING ON SELF-ASSESSED FUNCTION AND QUALITY OF LIFE IN POSTMENOPAUSAL WOMEN WITH MILD KNEE OSTEOARTHRITIS - A RANDOMISED CONTROLLED TRIAL WITH 12-MONTH FOLLOW-UP

by

Munukka M, Waller B, Häkkinen A, Nieminen M.T, Lammentausta E, Kujala U.M,
Paloneva J, Kautiainen H, Kiviranta I & Heinonen A. 2018

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III

PHYSICAL ACTIVITY IS RELATED WITH CARTILAGE QUALITY IN WOMEN WITH KNEE OSTEOARTHRITIS

by

Munukka M, Waller B, Häkkinen A, Nieminen M.T, Lammentausta E, Kujala U.M,
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Physical Activity Is Related with Cartilage Quality in Women with Knee Osteoarthritis

Matti Munukka¹, Benjamin Waller¹, Arja Häkkinen^{1,2}, Miika T. Nieminen^{3,4,5},
Eveliina Lammentausta⁴, Urho M. Kujala¹, Juha Paloneva⁶, Hannu Kautiainen^{7,8},
Ilkka Kiviranta⁹, and Ari Heinonen¹

¹Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland; ²Department of Physical Medicine and Rehabilitation, Central Finland Central Hospital, Jyväskylä, Finland; ³Research Unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland; ⁴Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland; ⁵Medical Research Center, University of Oulu and Oulu University Hospital, Oulu, Finland; ⁶Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland; ⁷Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland; ⁸Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland; ⁹Department of Orthopaedics and Traumatology, University of Helsinki, and Helsinki University Hospital, Helsinki, Finland

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Matti Munukka¹, Benjamin Waller¹, Arja Häkkinen^{1,2}, Miika T. Nieminen^{3,4,5}
Eveliina Lammentausta⁴, Urho M. Kujala¹, Juha Paloneva⁶, Hannu Kautiainen^{7,8}
Ilkka Kiviranta⁹, and Ari Heinonen¹

1. Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland
2. Department of Physical Medicine and Rehabilitation, Central Finland Central Hospital, Jyväskylä, Finland
3. Research Unit of Medical Imaging, Physics and Technology, University of Oulu, Oulu, Finland
4. Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland
5. Medical Research Center, University of Oulu and Oulu University Hospital, Oulu Finland
6. Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland
7. Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland
8. Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland
9. Department of Orthopaedics and Traumatology, University of Helsinki, and Helsinki University Hospital, Helsinki, Finland

Corresponding author: MSc Matti Munukka. University of Jyväskylä, Department of Health Sciences, P.O. Box 35, FI-40014 University of Jyväskylä, Finland. Phone: +358408053606. E-mail: matti.munukka@jyu.fi

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Abstract

Purpose: To study the relationship between 12-month leisure-time physical activity (LTPA) level and changes in estimated biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis (OA). **Methods:** Originally 87 volunteer postmenopausal women, aged 60-68 years, with mild knee OA (Kellgren Lawrence I/II and knee pain) participated in a randomised controlled, 4-month aquatic training trial (RCT), after which 76 completed the 12-month post-intervention follow-up period. Self-reported LTPA was collected along the 12-month period using a diary from which metabolic equivalent task hours (MET_h) per month were calculated. Participants were divided into MET_h tertiles: 1=lowest (n=25), 2=middle (n=25) and 3=highest (n=26). The biochemical composition of the cartilage was estimated using transverse relaxation time (T₂) mapping sensitive to the properties of the collagen network and delayed gadolinium-enhanced magnetic resonance imaging of the cartilage (dGEMRIC index) sensitive to the cartilage glycosaminoglycan (GAG) content. Secondary outcomes were cardiorespiratory fitness, isometric knee extension and flexion force and the knee injury and osteoarthritis outcome questionnaire (KOOS). **Results:** During the 12-month follow-up period, there was a significant linear relationship between higher LTPA level and increased dGEMRIC index changes in the posterior region of interest (ROI) of the lateral (p=0.003 for linearity) and medial (p=0.006) femoral cartilage. Furthermore, these changes were seen in the posterior lateral femoral cartilage superficial (p=0.004) and deep (p=0.007) ROIs and in the posterior medial superficial ROI (p<0.001). There was no linear relationship between LTPA level and other measured variables. **Conclusions:** These results suggest that higher LTPA level is related to regional increases in estimated GAG content of tibiofemoral cartilage in

postmenopausal women with mild knee OA as measured with dGEMRIC index during a 12-month period.

Key Words: Cartilage composition; Leisure-time physical activity; MET; Quantitative magnetic resonance imaging; Postmenopausal women; Follow-up study

ACCEPTED

INTRODUCTION

Knee osteoarthritis (OA) is a leading cause of pain and disability (11) and has significant socio-economical costs globally as it accounts for 83% of the total OA burden (36). Early OA causes changes in the biochemical composition of cartilage, such as loss of integrity of the collagen matrix and decrease in glycosaminoglycan (GAG) content (6). There is no known cure for OA, and thus, the main goal of OA management is pain relief and improving physical function (20). Therapeutic exercise, either land- or water-based, has been shown to evoke acute positive post-treatment effects on these goals (5, 39). However, while the effects of therapeutic exercise on pain are lost six months after the cessation of the exercise, small but significant improvements in self-reported physical function are sustained up to 24 months (5).

Active lifestyle with exercise has been shown to be beneficial for the maintenance of the biomechanical properties of cartilage both in healthy humans (31, 32, 34) and animals (13, 14). Thus, physical activity could be effective for the maintenance of cartilage health. Studies of the immediate post-treatment effects of exercise interventions on human cartilage are sparse, but show that the loading created by the exercise interventions can improve the estimated biochemical composition of tibiofemoral (24, 28) and patellofemoral (16) cartilage. In addition to positive cartilage responses observed in these studies (16, 24, 28), impact (16, 23), aquatic (24) and neuromuscular (28) exercise is shown not to be harmful for the estimated biochemical composition of the knee articular cartilage in population with mild knee OA (16, 23, 24) or at high risk of developing knee OA (28). Also, exercise is well tolerated in these populations (16, 23, 24, 28). Furthermore, Teichtal *et al.* (31) observed in a longitudinal follow-up study with

healthy population that over two years of vigorous physical activity is associated with a reduced rate of patella cartilage loss and has a trend towards a reduced risk for worsening patella cartilage defects.

In osteoarthritic population, there are no known long-term follow-up studies investigating the relationship between knee articular cartilage and LTPA. Therefore, the aim of the present study was to investigate the relationship between 12-months of LTPA and the biochemical composition of tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis.

METHODS

Study design

This study was a 12-month follow-up to our previously reported 4-month registered randomised controlled trial (ISRCTN65346593) with two experimental arms: 1) aquatic resistance training and 2) control (24). Therefore, the term “original intervention” is used to mean the period of 4-month RCT and “follow-up” denotes to the 12-month period after the end of the intervention and is the focus of the current study. This analysis, which exploited the data from the previous intervention study, followed the published protocol without changes (38). The participants were women aged 60-68 years with mild knee OA and were divided into tertiles based on their average monthly LTPA (METH) during the follow-up period. The study protocol (Dnro 19U/2011) was approved by the Ethics Committee of the Central Finland Health Care District and conforms to the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Study participants

Originally, postmenopausal women experiencing knee pain on most days from the Jyväskylä region in Central Finland were voluntarily recruited through advertisements in local newspapers. Preliminary eligibility to the original intervention was assessed using a structured telephone interview (n=323), followed by evaluation of osteoarthritis severity in the tibiofemoral joint with radiographs (confirmed mild tibiofemoral joint OA grades I or II according to the Kellgren Lawrence classification) (n=180) and finally through medical screening (n=111). In total 87 participants were included in the original intervention study. Inclusion criteria to the original intervention were: 1) a postmenopausal woman aged 60-68 years, 2) experiencing knee pain on most days, 3) participating in no more intensive exercise than brisk walking \leq twice a week, 4) radiographic changes in tibiofemoral joint K/L I or II, 5) no cancer or chemotherapy prior to the study, 6) no medical contraindications or other limitations to full participation in an intensive aquatic training program and 7) complete T2 data. Exclusion criteria included: 1) a T-score $<$ -2.5 (indicating osteoporosis) (12) measured from the femoral neck using dual-energy X-ray absorptiometry (DXA), 2) resting knee pain visual analogue scale (VAS) $>$ 50/100, 3) a body mass index (BMI) of $>$ 34 kg/m² (due to confounding factors related to obesity in relation to original intervention), 4) surgery of the knee due to trauma or knee instability, 5) meniscectomy within the last 12 months, 6) inflammatory joint disease, 7) intra-articular steroid injections in the knee during the previous 12 months, 8) contraindications to MRI and 9) allergies to contrast agents or renal insufficiency. Additionally, in this study, all LTPA diaries needed to be returned from the follow-up period. In total 84 participants attended the 12-month post-intervention follow-up study.

Leisure-time physical activity diary

Each participant's LTPA (26) from the 12-month study period was recorded using a LTPA diary implemented in our previous studies (16, 23, 24). Participants marked their LTPAs each day for 12 months and were instructed only to mark activities that lasted at least 20 minutes at a time (i.e. duration, type and intensity). Duration was reported in minutes and was converted into hours. Metabolic equivalent task (MET-hours) per month was calculated by multiplying each marked activity by self-evaluated intensity (1 = Light, 2 = Moderate, 3 = Vigorous) according to Ainsworth et al. 2011 (1). Participants were divided into tertiles based on their average monthly METh for the 12-month period: lowest, middle and highest tertile (Table 1). Compliance for returning all diaries from the follow-up period was 97.4%. An example LTPA diary is provided in the supplemental digital content (see appendix A, Supplemental Digital Content 1, example Leisure-time physical activity diary from one follow-up month, <http://links.lww.com/MSS/A877>).

Primary outcome measures

Primary outcome measures for this study, T2 relaxation time (T2) mapping (milliseconds, ms) and the delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC index, ms), were measured using a Siemens Magnetom Symphony Quantum 1.5-T scanner (Siemens AG, Medical Solutions, Erlangen, Germany). These methods provide information on the response of tibiofemoral cartilage to physiological loading (21, 28). T2 is a surrogate for the properties of the collagen network with lower values corresponding to better integrity and orientation of the collagen fibres and the hydration of the articular cartilage (18, 30). dGEMRIC index measures estimated GAG content of the knee articular cartilage with higher values

corresponding to higher estimated GAG concentration (2). The MRIs were performed by external radiographers and segmentation was performed blinded to original group allocation. Single sagittal slice images from the centre of the medial and lateral femoral condyles were taken from the affected knee with the highest K/L grade for both T2 and dGEMRIC index measurements. In cases of identical grading bilaterally, the right knee was imaged. Images were manually segmented using an in-house MATLAB application with built-in motion correction for dGEMRIC (Mathworks, Inc. Natick, MA, USA). In this study, we divided the femoral cartilage into three ROIs: anterior, central and posterior. As illustrated in Figure 1, anterior and posterior borders of the anterior and posterior meniscus were used as landmarks to define the margins of the femoral and tibial cartilage ROIs. dGEMRIC indices were corrected for BMI (33). Precision, scan-rescan, (CV_{RMS}) of dGEMRIC in asymptomatic subjects is 7% for full-thickness ROIs and 5% for bulk cartilage (22). In our laboratory, the inter-observer error (CV_{RMS}) for T2 full-thickness ROIs was 1.3% to 3.3% and 2.8% to 4.0% for dGEMRIC. The full MRI protocol and example images are provided in the supplemental digital content (see appendix B, Supplemental Digital Content 2, MRI protocol and example of image segmentations, <http://links.lww.com/MSS/A878>).

Secondary outcomes

Physical performance

Cardiorespiratory fitness (VO_2 peak, ml/kg/min) was estimated using the UKK 2 km walking test (UKK Institute, Tampere, Finland) (19) and isometric knee extension and flexion force (N/kg) of the affected knee was measured at a 60 degree angle using an adjustable dynamometer chair

(Good strength; Metitur Ltd, Jyväskylä Finland) (29). Physical performance measurements have been described in detail in our study protocol (38).

Self-assessed impact of OA symptoms

Self-assessed impact of OA on pain, other symptoms, activities of daily living, sports and recreations and knee-related quality of life were assessed using the validated Finnish (15) Likert version of the knee injury and osteoarthritis outcome score (KOOS) questionnaire (27). Scores for each domain range from 0 to 100, with the score of 0 indicating extreme and 100 no knee problems.

Statistical analyses

The results are presented as means and standard deviations (SD). Statistical significance for the hypothesis of linearity between physical activity tertiles (lowest, middle and highest) with cartilage and physical performance traits were evaluated by using analysis of variance (ANOVA) and analysis of covariance (ANCOVA). T2 was adjusted for baseline value, height and weight. dGEMRIC index (already adjusted for BMI) and secondary outcomes were adjusted for baseline value only. The normality of the variables was tested by using the Shapiro-Wilk W test. Since two participants (2.6%) had missing LTPA diary data, last observation carried forward method was used. Statistical analyses were performed using statistical software (Stata, release 14.1, StataCorp, College Station, Texas).

RESULTS

During the 12-month follow-up, eight (10%) participants dropped out of the study. One participant died due to diagnosed cancer and one due to unknown reasons. In addition, one participant withdrew due to activated Ménière's disease, two due to personal reasons, one due to hip arthroplasty, one due to radiotherapy for breast cancer and one did not return the physical activity diaries from the entire follow-up period. Therefore, 76 (90%) participants completed the 12-month follow-up period. The division into METH tertiles was: 1=lowest (n=25), 2=middle (n=25) and 3=highest (n=26). Importantly, there was no difference between the LTPA METH tertiles according to the original intervention study groups (i.e. members of the training and control group) in the beginning or during the follow-up (Table 1).

Demographic and clinical characteristics of the study participants according to the LTPA (METH) in the beginning of the follow-up period (i.e. baseline) are shown in Table 2. At the baseline, there was a linear inverse relationship between body mass ($p<0.001$), BMI ($p<0.001$), cardiorespiratory fitness (VO_2 peak, $p<0.001$), muscle force (knee extension, $p<0.001$, knee flexion, $p=0.011$) and LTPA level. Most common LTPAs during the 12-month follow-up period were walking (including Nordic walking) (mean: 1h 5min/week, 1h 38min/week and 3h/week in the tertiles, respectively), and LTPA described as “other” (e.g. gardening and cleaning) (mean: 55min/week, 1h 13min/week and 1h 28min/week in the tertiles, respectively). Average monthly MET hours in LTPA tertiles for each follow-up month are provided in the supplemental digital content (see appendix C, Supplemental Digital Content 3, Average monthly MET hours in leisure time physical activity tertiles, <http://links.lww.com/MSS/A879>).

To ensure accuracy, each MRI image was inspected for quality, and exclusion required full agreement within the research group. All T2 data sets were included in the analysis. One complete dGEMRIC index data set was not measured due to participant's rejection of contrast agent injection. Additionally, from the dGEMRIC index, 21 participants had movement artifact in the medial condyle, while in the lateral condyle, 17 participants had either artery-flow pulsating artifact or movement artifact and one inaccurate location of the slice compared to baseline image. These data sets were therefore missing from the final analysis. In total 54 and 57 complete datasets for medial and lateral condyles respectively were available for quantitative dGEMRIC analysis.

T2 and dGEMRIC index change during the 12-month follow-up and p-value for linearity in relation to LTPA level are given in Table 3. In knee cartilage regions, there was a statistically significant linear relationship showing that dGEMRIC index in posterior ROI of the lateral ($p=0.003$) and medial ($p=0.006$) femoral cartilage increased with higher LTPA level during 12-month period. Furthermore, these changes were seen in the posterior lateral femoral cartilage superficial ($p=0.004$) and deep ($p=0.007$) ROIs and in the posterior medial superficial ROI ($p<0.001$) (Figure 2). No linear relationship was observed between LTPA level and changes in T2 relaxation time (Table 3), physical performance characteristics or self-assessed impact of OA symptoms (KOOS) during 12 months (Table 4).

DISCUSSION

To our knowledge, we are the first to demonstrate that long-term (12-month) LTPA level is related to regional increases in estimated GAG content of tibiofemoral cartilage in postmenopausal women with mild knee OA as measured with dGEMRIC index. This linear relationship was observed in the posterior region of medial and lateral femoral cartilage, which is less loaded during activities of daily living than the central region (37). Cardiorespiratory fitness, muscle force and all KOOS dimensions remained at the follow-up initiation level, and no linearity with LTPA tertiles was observed during 12 months.

Our results indicate that people with higher levels of LTPA during the 12-month follow-up period also had larger increases in the dGEMRIC index (i.e. estimated GAG content) within the cartilage of the posterior ROI of the medial and lateral femoral condyle. It has been suggested that in the dGEMRIC index, higher values correspond to higher knee articular cartilage GAG concentration (2). This can be interpreted to mean that when exposed to sufficient loading stimulus and environment, all chondrocytes, including cells extracted from OA cartilage, have a latent loading adaptation ability to regenerate and proliferate matrix (e.g. GAGs and collagen) (10, 31). Furthermore, our results are suggesting that persons with mild knee OA may have a lower threshold for chondrocyte adaptation in the posterior region of the femoral cartilage, which is less loaded during the activities of daily living compared to the central region. Our previous findings support this suggestion (24). Aforementioned results are also supported by several animal (3, 13, 14) and human studies in healthy population (31, 32, 34) and in people at a high risk of developing knee OA following surgery for meniscal injury (28), showing the beneficial

relationship between a physically active lifestyle and the maintenance of the biochemical properties of cartilage.

It has been suggested that GAG loss is an early feature in OA, and it occurs primarily in the superficial region of cartilage (4, 25), but the nature of responses and the exact region in osteoarthritic cartilage to exercise is not yet fully understood. In our present study, the dGEMRIC index (i.e. estimated GAG content) responded to LTPA similarly in the superficial and deep cartilage (i.e. full-thickness) in the posterior ROI of medial and lateral femoral cartilage. Our results are in line with the study by Hawezi *et al.* (9), who also showed that a change in the dGEMRIC index due to a change in the physical activity level occurred both in the superficial and deep cartilage regions (i.e. full-thickness) in people with a risk of developing OA. However, this full-thickness effect may be at least partly explained by the relatively large decrease in the dGEMRIC index seen in the deep ROI of the posterior condyle. Additionally, the diffusion of the contrast agent is influenced by the cartilage thickness, where thinner cartilage results in a lower dGEMRIC index (8). In our study, cartilage thickness was not measured, leaving this issue open to speculation and for further investigation.

In our study, no linear relationship was observed between a 12-month period of LTPA and changes in T2 relaxation time. T2 measures different cartilage attributes than dGEMRIC index, indicating that a low T2 value corresponds to better integrity and orientation of the collagen fibres and a decrease in the hydration of the articular cartilage (18, 30). In our previous exercise intervention study we found that a 4-month progressive aquatic resistance training program (i.e. full range of motion with high repetition low shear and compressive cyclic forces) improved the

estimated biochemical composition of the medial posterior tibiofemoral cartilage as measured with T2 (24). The benefit of this type of loading pattern for integrity and orientation of the collagen fibres is also supported by our previous land-based RCTs (16, 23). Koli *et al.* (16) showed that a 12-month progressively implemented high-impact and intensive jumping exercise (i.e. impact exercises were shear with moderate compression in the patellofemoral joint) in postmenopausal women with mild knee OA improved the estimated biochemical composition of the patellar cartilage as measured with T2. Using the same intensive intervention, Multanen *et al.* (23) showed that no positive or negative effect was observed in the biochemical composition of tibiofemoral cartilage (i.e. T2 or dGEMRIC index). The LTPAs may not have exposed the knee joint to optimal and sufficient intensity and loading to cause adaptation in the integrity of the collagen-interstitial water environment (T2) in the tibiofemoral cartilage. However, GAG concentration (i.e. dGEMRIC index) may be more responsive to intermittent impact and compression type of loading in people with mild tibiofemoral knee OA and may therefore partly explain the findings of this study. This explanation is also supported by Roos and Dahlberg 2005 (28). More controlled (type of exercise, loading, frequency, duration and intensity) exercise interventions are needed in order to determine the most optimal loading and intensity for improving overall cartilage quality in osteoarthritic population.

In this study, walking (including Nordic walking) accounted for 40% of the total LTPA.

Gait on level surface requires knee range of motion from nearly full extension to 60-65 degree flexion (37), and knee flexion of over 90 degrees is required to produce contact between posterior ROI of femur and central tibia (7). Therefore, the biomechanics of gait do not solely explain why an increase in dGEMRIC index was observed in the posterior ROIs of cartilage. The

average peak knee joint loading during normal gait is in the range of 2 to 4.5 times body weight (17, 40). Thus, it can be speculated that the effects of intermittent impact and compressive loading during gait to knee central cartilage might have had favorable adjacent effects on less customary loaded posterior cartilage (e.g. trough pressure changes and muscle contraction) with a higher LTPA level. This higher repetitive mechanical stimulus might have been sufficient to cause beneficial changes, such as improved fluid flow and nutrient diffusion in the posterior ROI of the femoral cartilage. On the other hand, repetitive knee bending exposure (i.e. deep knee bending or kneeling for 30 minutes or more) has been associated with an increased risk of prevalent cartilage lesion especially in patellofemoral compartment in males and females between the ages 45 and 55 with a risk for OA (35). In our study, the activity described as “other” (e.g. gardening and cleaning) accounted for 23% of the total LTPA. These activities might have included non-repetitive uncustomary loading to the knee (i.e. higher knee flexion with larger range of motion), which can be hypothesised to have caused beneficial changes in less loaded posterior ROI of femoral cartilage. In our previous study (24) we discussed that the chondrocytes in the posterior region of the femoral cartilage in persons with mild knee OA may have a lower threshold for adaption compared to the central region, and in contrast, the chondrocytes in the central region of the femur and tibia cartilage may require a higher or atypical loading compared to customary loading in order to stimulate an adaptive response. Thus, posterior less customary loaded medial and lateral femoral condyle cartilage might be more responsive to light exercise than the central cartilage. Therefore, even light LTPA performed regularly in the long-term may be sufficient enough to positively stimulate the less customary loaded posterior region of medial and lateral femoral cartilage, which was observed in our study

as increased estimated GAG concentration. Also, LTPA even at the highest level was well tolerated and did not increase clinical symptoms in women with mild knee OA.

The strengths of this study include the long-term follow-up period (12-months) and high adherence to the end measurements with no harms observed as LTPA level increased. In addition, each participant's daily physical activity was monitored each day throughout the whole 12-month follow-up period. Strict imaging procedure and segmentation rules ensured good stability and repeatability of the T2 relaxation time and dGEMRIC indices. This limits the possible effects of the magic angle (particularly T2) and partial volume effects. The long imaging time in dGEMRIC mapping might result in motion artefact, which was controlled for in our study by using a motion correction technique built into the in-house software as well as a strict inclusion/exclusion criterion for image quality (i.e. excessive movement and pulsating artefact). This study also had some minor limitations, which were related to the MRI imaging and analysis technique. We used a 1.5 tesla scanner, whereas a 3.0 tesla scanner would have produced better spatial resolution and a higher signal-to-noise ratio. In some cases occasionally thinned and deteriorated cartilage and movement (despite the motion correction technique) or pulsating artery artefact prevented reliable segmentation of cartilage resulting in lost data. Also, the single-slice segmentation method utilised in this study assesses only a restricted region of the cartilage, whereas the multi-slice method might have produced a more comprehensive representation of the tibiofemoral cartilage. The segmentation software automatically divided cartilage of each full-thickness ROI into deep and superficial compartments (50%/50%). However, due to the 1.5T scanner used, segmented cartilage thickness ranged from two to five voxels, thus reducing the spatial accuracy. Due to the strict inclusion criteria in the original

intervention study (24), our results cannot be directly applied to people with later stage OA or older or extremely obese women and men. Finally, the authors acknowledge that so far there is no “golden standard” method to measure how exercise directly affects the biochemical composition of cartilage in vivo. Therefore, the different qMRI parameters and their interactions are not yet fully understood (2) and further investigations about the interaction between exercise, cartilage and these parameters are needed.

In conclusion, these results suggest that higher LTPA level is related to regional increases in estimated GAG content of tibiofemoral cartilage as measured with dGEMRIC index during a 12-month period. These results have an important role when assessing physical activity levels for cartilage quality related exercise intervention studies and also in clinical rehabilitation in postmenopausal women with mild tibiofemoral knee OA.

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ACCEPTED

References

1. Ainsworth BE, Haskell WL, Herrmann SD, et al. 2011 Compendium of Physical Activities: a second update of codes and MET values. *Med Sci Sports Exerc.* 2011; 43(8):1575-81.
2. Binks D, Hodgson R, Ries M, et al. Quantitative parametric MRI of articular cartilage: a review of progress and open challenges. *Br J Radiol.* 2013; 86(1023):20120163.
3. Brismar BH, Lei W, Hjerpe A, Svensson O. The effect of body mass and physical activity on the development of guinea pig osteoarthritis. *Acta Orthop Scand.* 2003; 74(4):442-8.
4. Dumond H, Presle N, Pottier P, et al. Site specific changes in gene expression and cartilage metabolism during early experimental osteoarthritis. *Osteoarthritis Cartilage.* 2004; 12(4):284-95.
5. Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: a Cochrane systematic review. *Br J Sports Med.* 2015; 49(24):1554-7.
6. Goldring MB, Goldring SR. Articular cartilage and subchondral bone in the pathogenesis of osteoarthritis. *Ann N Y Acad Sci.* 2010; 1192(1):230-7.
7. Goyal K, Tashman S, Wang JH, Li K, Zhang X, Harner C. In vivo analysis of the isolated posterior cruciate ligament-deficient knee during functional activities. *Am J Sports Med.* 2012; 40(4):777-85.
8. Hawezi ZK, Lammentausta E, Svensson J, Dahlberg LE, Tiderius CJ. In vivo transport of Gd-DTPA2- in human knee cartilage assessed by depth-wise dGEMRIC analysis. *J Magn Reson Imaging.* 2011; 34(6):1352-8.
9. Hawezi ZK, Lammentausta E, Svensson J, Roos EM, Dahlberg LE, Tiderius CJ. Regional dGEMRIC analysis in patients at risk of osteoarthritis provides additional information about activity related changes in cartilage structure. *Acta Radiol.* 2015; 0284185115591237.

10. Jeon JE, Schrobback K, Meinert C, Sramek V, Hutmacher DW, Klein TJ. Effect of preculture and loading on expression of matrix molecules, matrix metalloproteinases, and cytokines by expanded osteoarthritic chondrocytes. *Arthritis Rheum.* 2013; 65(9):2356-67.
11. Johnson VL, Hunter DJ. The epidemiology of osteoarthritis. *Best Pract Res Clin Rheumatol.* 2014; 28(1):5-15.
12. Kanis JA, McCloskey EV, Johansson H, Oden A, Melton LJ, Khaltsev N. A reference standard for the description of osteoporosis. *Bone.* 2008; 42(3):467-75.
13. Kiviranta I, Tammi M, Jurvelin J, Arokoski J, Säämänen A, Helminen HJ. Articular cartilage thickness and glycosaminoglycan distribution in the young canine knee joint after remobilization of the immobilized limb. *J Orthop Res.* 1994; 12(2):161-7.
14. Kiviranta I, Tammi M, Jurvelin J, Saamanen AM, Helminen HJ. Moderate running exercise augments glycosaminoglycans and thickness of articular cartilage in the knee joint of young beagle dogs. *J Orthop Res.* 1988; 6(2):188-95.
15. Koli J, Multanen J, Häkkinen A, Kiviranta I, Kujala U, Heinonen A. Reliability of the Finnish versions of WOMAC and KOOS forms for knee osteoarthritis. *Physiotherapy.* 2011; 97(Suppl. S1):D203-4.
16. Koli J, Multanen J, Kujala UM, et al. Effects of Exercise on Patellar Cartilage in Women with Mild Knee Osteoarthritis. *Med Sci Sports Exerc.* 2015; 47(9):1767-74.
17. Kumar D, Manal KT, Rudolph KS. Knee joint loading during gait in healthy controls and individuals with knee osteoarthritis. *Osteoarthritis Cartilage.* 2013; 21(2):298-305.
18. Lammentausta E, Kiviranta P, Nissi M, et al. T2 relaxation time and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) of human patellar cartilage at 1.5 T and 9.4 T: Relationships with tissue mechanical properties. *J Orthop Res.* 2006; 24(3):366-74.

19. Laukkanen R, Oja R, Pasanen M, Vuori I. Criterion validity of a two-kilometer walking test for predicting the maximal oxygen uptake of moderately to highly active middle-aged adults. *Scand J Med Sci Sports*. 1993; 3(4):267-72.
20. McAlindon T, Bannuru R, Sullivan M, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage*. 2014; 22(3):363-88.
21. Mosher TJ, Liu Y, Torok CM. Functional cartilage MRI T2 mapping: evaluating the effect of age and training on knee cartilage response to running. *Osteoarthritis and Cartilage*. 2010; 18(3):358-64.
22. Multanen J, Rauvala E, Lammentausta E, et al. Reproducibility of imaging human knee cartilage by delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) at 1.5 Tesla. *Osteoarthritis Cartilage*. 2009; 17(5):559-64.
23. Multanen J, Nieminen MT, Häkkinen A, et al. Effects of High-Impact Training on Bone and Articular Cartilage: 12-Month Randomized Controlled Quantitative MRI Study. *J Bone Miner Res*. 2014; 29(1):192-201.
24. Munukka M, Waller B, Rantalainen T, et al. Efficacy of progressive aquatic resistance training for tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis: a randomised controlled trial. *Osteoarthritis Cartilage*. 2016; 24(10):1708-17.
25. Pfander D, Swoboda B, Kirsch T. Expression of early and late differentiation markers (proliferating cell nuclear antigen, syndecan-3, annexin VI, and alkaline phosphatase) by human osteoarthritic chondrocytes. *Am J Pathol*. 2001; 159(5):1777-83.
26. Physical Activity Guidelines Advisory Committee. Physical activity guidelines advisory committee report, 2008. *Washington, DC: US Department of Health and Human Services*. 2008:A1-H14.

27. Roos EM, Roos H, Ekdahl C, Lohmander L. Knee injury and Osteoarthritis Outcome Score (KOOS)-validation of a Swedish version. *Scand J Med Sci Sports*. 1998; 8(6):439-48.
28. Roos EM, Dahlberg L. Positive effects of moderate exercise on glycosaminoglycan content in knee cartilage: a four-month, randomized, controlled trial in patients at risk of osteoarthritis. *Arthritis Rheum*. 2005; 52(11):3507-14.
29. Sipilä S, Multanen J, Kallinen M, Era P, Suominen H. Effects of strength and endurance training on isometric muscle strength and walking speed in elderly women. *Acta Physiol Scand*. 1996; 156(4):457-64.
30. Subburaj K, Kumar D, Souza RB, et al. The acute effect of running on knee articular cartilage and meniscus magnetic resonance relaxation times in young healthy adults. *Am J Sports Med*. 2012; 40(9):2134-41.
31. Teichtahl AJ, Wluka AE, Forbes A, et al. Longitudinal effect of vigorous physical activity on patella cartilage morphology in people without clinical knee disease. *Arthritis Rheum*. 2009; 61(8):1095-102.
32. Tiderius CJ, Svensson J, Leander P, Ola T, Dahlberg L. dGEMRIC (delayed gadolinium-enhanced MRI of cartilage) indicates adaptive capacity of human knee cartilage. *Magn Reson Med*. 2004; 51(2):286-90.
33. Tiderius C, Hori M, Williams A, et al. dGEMRIC as a function of BMI. *Osteoarthritis Cartilage*. 2006; 14(11):1091-7.
34. Van Ginckel A, Baelde N, Almqvist K, Roosen P, McNair P, Witvrouw E. Functional adaptation of knee cartilage in asymptomatic female novice runners compared to sedentary controls. A longitudinal analysis using delayed gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC). *Osteoarthritis Cartilage*. 2010; 18(12):1564-9.

35. Virayavanich W, Alizai H, Baum T, et al. Association of frequent knee bending activity with focal knee lesions detected with 3T magnetic resonance imaging: data from the osteoarthritis initiative. *Arthritis Care Res (Hoboken)*. 2013; 65(9):1441-8.
36. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2013; 380(9859):2163-96.
37. Walker CR, Myles C, Nutton R, Rowe P. Movement of the knee in osteoarthritis. The use of electrogoniometry to assess function. *J Bone Joint Surg Br*. 2001; 83(2):195-8.
38. Waller B, Munukka M, Multanen J, et al. Effects of a progressive aquatic resistance exercise program on the biochemical composition and morphology of cartilage in women with mild knee osteoarthritis: protocol for a randomised controlled trial. *BMC Musculoskelet Disord*. 2013; 14:10.1186/1471-2474-14-82.
39. Waller B, Ogonowska-Slodownik A, Vitor M, et al. Effect of therapeutic aquatic exercise on symptoms and function associated with lower limb osteoarthritis: systematic review with meta-analysis. *Phys Ther*. 2014; 94(10):1383-95.
40. Winby CR, Lloyd DG, Besier TF, Kirk TB. Muscle and external load contribution to knee joint contact loads during normal gait. *J Biomech*. 2009; 42(14):2294-300.

FIGURE LEGENDS:

Figure 1. Illustration of the region of interests (ROIs) in the full-thickness femoral and tibial cartilage. Midlines split both femoral and tibial cartilage into superficial and deep sections. ROIs were segmented according to the landmarks as follows for central femoral cartilage: from the anterior end of anterior meniscus (arrow 1) to the posterior end of the posterior meniscus (arrow 2) and for central tibial cartilage: from the posterior end of anterior meniscus (arrow 3) to the anterior end of the posterior meniscus (arrow 4).

Figure 2. dGEMRIC index change during the 12-month follow-up from femoral posterior lateral and medial superficial and deep ROIs according to LTPA (Metabolic Equivalent hour, MET_h) tertiles.

SUPPLEMENTAL DIGITAL CONTENT:

Appendix A.docx—An example Leisure-time physical activity diary from one follow-up month

Appendix B.docx—MRI protocol and example of image segmentations

Appendix C.docx—Average monthly MET hours in leisure time physical activity tertiles

Figure 1

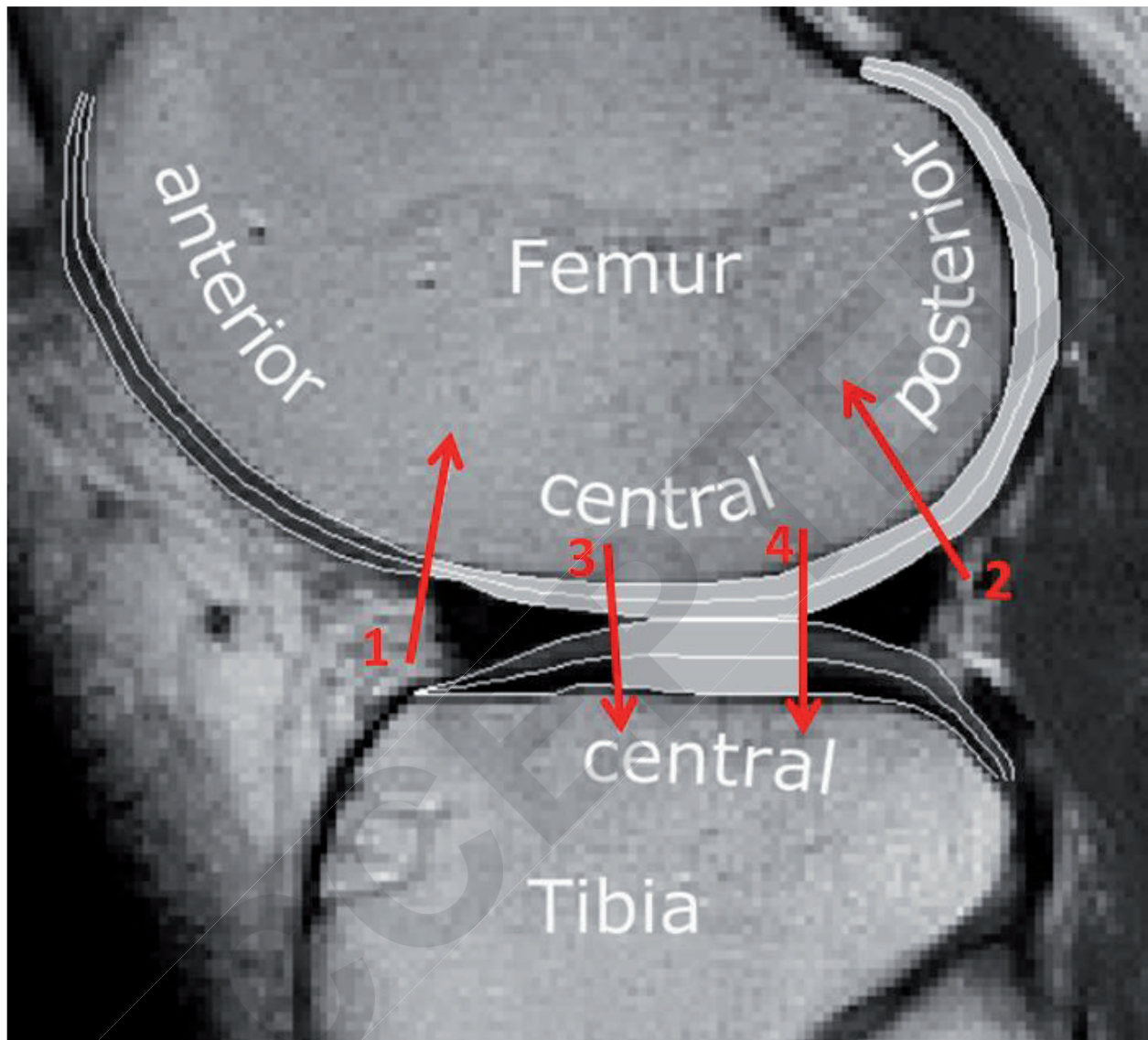


Figure 2

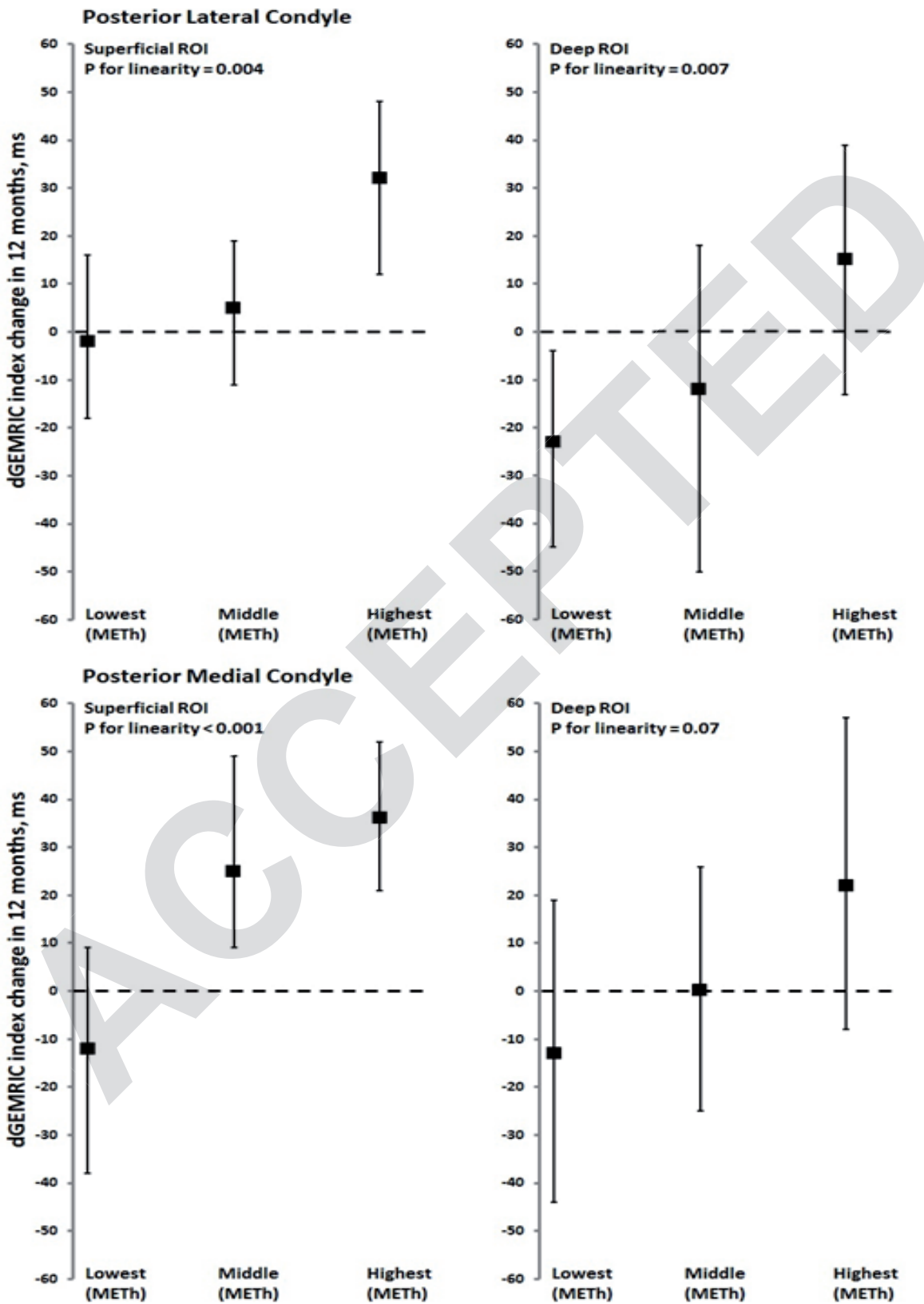


Table 1. Average monthly METH for the follow-up period.

	Lowest METH (n=25)	Middle METH (n=25)	Highest METH (n=26)
All participants			
METH, mean (SD)	52 (15)	97 (14)	155 (29)
Original intervention group			
Number (%)	16 (64.0)	12 (48.0)	11 (42.3)
METH, mean (SD)	53 (15)	96 (14)	156 (36)
Original control group			
Number (%)	9 (36.0)	13 (52.0)	15 (57.7)
METH, mean (SD)	49 (15)	98 (15)	155 (26)

Original intervention group: Intervention group of the original RCT design. Original control group: Control group of the original RCT design.

Table 2. Demographic and clinical characteristics of the participants at the beginning of 12-month follow-up.

	Lowest METh (n=25)	Middle METh (n=25)	Highest METh (n=26)	P for linearity
Age (years)	64 (2)	64 (3)	65 (2)	0.39
Height (cm)	162 (5)	161 (5)	163 (4)	0.47
Body mass (kg)	76.4 (10.8)	69.1 (10.8)	65.3 (9.1)	<0.001
Body mass index (kg/m ²)	28.9 (3.4)	26.6 (3.8)	24.5 (3.0)	<0.001
Cartilage traits				
T2, (ms) Femur				
Lateral condyle: Central	52.1 (4.8)	51.8 (3.3)	54.7 (4.4)	0.053
Lateral condyle: Posterior	48.5 (4.3)	49.8 (3.7)	50.0 (3.3)	0.16
Medial condyle: Central	51.8 (6.6)	53.7 (3.6)	51.8 (5.1)	0.99
Medial condyle: Posterior	51.0 (4.3)	52.1 (3.5)	51.0 (5.4)	0.99
T2, (ms) Tibia				
Lateral plateau: Central	42.4 (9.1)	41.0 (6.8)	41.9 (9.2)	0.85
Medial plateau: Central	43.5 (5.3)	44.3 (3.8)	43.1 (4.8)	0.76
dGEMRIC index, (ms) Femur				
Lateral condyle: Central	419 (56)	425 (64)	433 (48)	0.70
Lateral condyle: Posterior	424 (66)	427 (85)	428 (54)	0.85
Medial condyle: Central	398 (53)	392 (77)	423 (44)	0.13

Medial condyle: Posterior	434 (66)	447 (68)	449 (63)	0.60
dGEMRIC index, (ms) Tibia				
Lateral plateau: Central	394 (83)	442 (94)	418 (79)	0.17
Medial plateau: Central	373 (61)	374 (73)	380 (48)	0.92

Physical performance

Cardiorespiratory fitness, (ml/kg/min)

Estimated VO ₂ peak	24.6 (3.9)	26.8 (5.9)	29.5 (4.1)	<0.001
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Muscle Force, (N/kg)

Knee extension	4.4 (0.8)	5.6 (1.2)	5.7 (1.4)	<0.001
Knee flexion	2.4 (0.5)	2.8 (0.7)	2.9 (0.9)	0.011

Clinical symptoms

KOOS, range 0-100mm

Pain	83 (11)	85 (11)	85 (11)	0.70
Other symptoms	80 (12)	80 (13)	81 (13)	0.72
ADL	86 (12)	88 (14)	88 (10)	0.66
Sport	67 (24)	69 (30)	73 (17)	0.33
QOL	72 (20)	76 (22)	76 (18)	0.50

Values are means (SD)

METH = metabolic equivalent task hour (Tertiles based on participants average monthly METH)

T2 = transverse relaxation time = high values correspond to compromised cartilage structure degeneration. dGEMRIC index = high values correspond to high glycosaminoglycan concentration.

KOOS = Knee Injury and Osteoarthritis Outcome Score, ADL= activities of daily living, Sport = sports and recreation, QOL = knee related quality of life

Table 3. Cartilage trait value change during 12-month follow-up from different anatomical regions according to Metabolic Equivalent (MET) values.

		Change to month 12, mean (95% CI)		
		Lowest METh (n=25)	Middle METh (n=25)	Highest METh (n=26)
T2, ms				
Femur				
Lateral condyle				
	Central	0.29 (-1.23 to 1.54)	0.62 (-0.58 to 1.89)	-0.62 (-2.07 to 0.45)
	Posterior	-0.97 (-2.17 to -0.003)*	-1.29 (-2.47 to 0.002)	-0.87 (-2.20 to 0.32)
Medial condyle				
	Central	-0.25 (-1.66 to 1.15)	-1.00 (-2.04 to -0.07)*	-0.13 (-1.57 to 1.22)
	Posterior	0.14 (-0.81 to 1.16)	-0.81 (-1.76 to 0.17)	0.05 (-0.86 to 0.95)
Tibia				
Lateral plateau				
	Central	-1.24 (-3.40 to 0.72)	-0.77 (-2.50 to 0.87)	-0.25 (-1.96 to 1.30)

Medial plateau				
Central	-0.86 (-2.32 to 0.55)	-0.15 (-1.56 to 1.09)	-0.68 (-2.26 to 0.81)	
dGEMRIC index[†], ms				
Femur				
Lateral condyle[†]				
Central	-8 (-22 to 5)	-14 (-31 to 4)	8 (-14 to 27)	
Posterior	-17 (-32 to -2)*	-8 (-35 to 12)	18 (-5 to 37)	
Medial condyle[§]				
Central	-7 (-23 to 10)	12 (-7 to 27)	9 (-5 to 24)	
Posterior	-17 (-39 to 6)	5 (-12 to 24)	24 (2 to 49)*	
Tibia				
Lateral plateau				
Central	-8 (-24 to 9)	-22 (-44 to 1)	2 (-15 to 21)	
Medial plateau				
Central	-17 (-34 to 4)	-13 (-42 to 11)	2 (-17 to 20)	

T2 = transverse relaxation time; ^a adjusted for baseline value, height and weight.

dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage; ^b adjusted for baseline value.

In T2 low values correspond to improved integrity and orientation of the collagen fibres and a decrease in hydration of articular

In dGEMRIC index, high values correspond to high glycosaminoglycan concentration.

[†]Missing data for dGEMRIC [‡]n=18, [§]n=22

* Within-group change was statistically significant at $p < 0.05$ level

Table 4. Physical performance and clinical symptoms change to month 12 according to Metabolic Equivalent (METh) values.

	Change to month 12, mean (95% CI)		
	Lowest METh (n=25)	Middle METh (n=25)	Highest METh (n=26)
Cardiorespiratory fitness (ml/kg/min)			
Estimated VO ₂ peak	-1.0 (-2.6 to 0.6)	-0.5 (-1.8 to 0.7)	-0.7 (-1.6 to 0.1)
Muscle force (N/kg)			
Knee extension	-0.1 (-0.3 to 0.1)	0.0 (-0.3 to 0.3)	0.0 (-0.3 to 0.2)
Knee flexion	-0.1 (-0.2 to 0.1)	0.0 (-0.2 to 0.1)	0.0 (-0.2 to 0.1)
KOOS (0-100)			
Pain	-0.8 (-5.1 to 3.5)	-2.4 (-5.2 to 0.3)	-1.5 (-6.9 to 3.9)
Other symptoms	1.0 (-3.2 to 5.2)	0.0 (-2.3 to 2.3)	0.4 (-3.2 to 4.1)
ADL	-1.00 (-4.7 to 2.7)	-1.4 (-6.0 to 3.2)	-1.9 (-4.8 to 0.9)
Sport	1.0 (-7.2 to 9.2)	2.4 (-4.2 to 9.0)	-2.7 (-9.9 to 4.6)
QOL	-1.0 (-7.9 to 5.9)	1.3 (-3.2 to 5.7)	-5.0 (-12.5 to 2.4)

KOOS = Knee injury and osteoarthritis outcome score, ADL= activities of daily living; Sport = sports and recreation; QOL = knee related quality of life

^a Adjusted for baseline

Appendix A: An example Leisure-time physical activity diary from one follow-up month

Leisure time physical activity: June 2013 (Follow-up)

Name: _____

Randomisation number: _____

Study ID: __/__/__/_/___/___/___/___/___

Mark into the leisure time physical activity diary all activities that you have **performed each day (at least 20 minutes at time)**. Mark also **how long the physical activity lasted (in minutes)** and how **exhausting** (light = *, moderate = **, Vigorous = ***) your activity was.

- * Light = no sweating, no heavy breathing
- ** Moderate = somewhat sweating or increased breathing
- *** Vigorous = heavy sweating or heavy breathing

Leisure time physical activity	Leisure time physical activity
1. Jogging or running	11. Home gymnastics
2. Orienteering	12. Supervised aerobic
3. Cross-country skiing	13. Dance in different forms
4. Bicycling	14. Water aerobics
5. Walking	15. Stretching
6. Nordic walking	16. Yoga/ Tai-Chi
7. Golf	17. Badminton
8. Swimming	18. Tennis
9. Rowing/canoeing	19. Downhill skiing
10. Gym/Circuit training	20. Horse riding
	21. Something else, what? _____

June 2013. Mark activities by using number code from the list in previous page, **duration in minutes** (at least 20 minutes) and **exhaustion**.

WK	Monday	Tuesday	Wednesday	Thursday	Friday
22	/	/	/	/	EXAMPLE! Activity: <u>5</u> Duration: <u>60</u> Intensity: <u>***</u>
23	3 Activity: _____ Duration: _____ Intensity: _____	4 Activity: _____ Duration: _____ Intensity: _____	5 Activity: _____ Duration: _____ Intensity: _____	6 Activity: _____ Duration: _____ Intensity: _____	7 Activity: _____ Duration: _____ Intensity: _____
24	10 Activity: _____ Duration: _____ Intensity: _____	11 Activity: _____ Duration: _____ Intensity: _____	12 Activity: _____ Duration: _____ Intensity: _____	13 Activity: _____ Duration: _____ Intensity: _____	14 Activity: _____ Duration: _____ Intensity: _____
25	17 Activity: _____ Duration: _____ Intensity: _____	18 Activity: _____ Duration: _____ Intensity: _____	19 Activity: _____ Duration: _____ Intensity: _____	20 Activity: _____ Duration: _____ Intensity: _____	21 Activity: _____ Duration: _____ Intensity: _____

26	Activity: _____ Duration: _____ Intensity: _____ _____ _____	24	Activity: _____ Duration: _____ Intensity: _____ _____ _____	25	Activity: _____ Duration: _____ Intensity: _____ _____ _____	26	Activity: _____ Duration: _____ Intensity: _____ _____ _____	27	28	Activity: _____ Duration: _____ Intensity: _____ _____ _____
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PREPRINT

Appendix B: MRI protocol and example of image segmentations

Prior to MRI imaging, the participant was advised to restrain from any strenuous physical activity during the 48 hours prior to the measurements to minimize possible transient changes in knee cartilage volume and composition. Participants were imaged at the same time of the day to avoid possible diurnal variation at the follow-up measurements.

The participants were imaged lying supine. The knee was positioned into the coil by adjusting inferior margin of patella according to the centre of line of the coil. The flexion angle and rotation of the knee was controlled by stabilising the ankle to a fixed position within the knee coil by using a leg holder and a custom made inflatable cushion. The cushion was specifically designed to stabilize the patella without causing any compression of the patellofemoral joint. The imaging session lasted 3 hours and included a standard clinical MRI series and T2 relaxation time followed by the dGEMRIC series.

T2 mapping was performed using a sagittal multi-slice multi-echo fast spin echo sequence (field of view (FOV) 140mm, acquisition matrix 256 x 256, repetition time (TR) 2090 ms, eight echo times (TE) between 13 and 104 ms, echo train length (ETL) 8, slice thickness 3 mm). The slices were positioned perpendicular to a line tangential to the posterior femoral condyles in the axial scout view. Two slices, each covering the central region of the medial and lateral condyles, were analysed.

For the dGEMRIC series, immediately after the clinical and T2 imaging, an intravenous injection of 0.4mL/kg (double dose) of Gd-DTPA²⁻ (Magnevist, Schering, Berlin) was administered. The amount of contrast agent administered was corrected for body weight at

each measurement point. This was appropriate because of the expected changes in body composition as a result of the intensive exercise intervention. In order to enhance the delivery of contrast agent into the knee cartilage, following administration of Gd-DTPA²⁻, the participants were instructed to perform 5 minutes of knee flexion-extension exercises in a sitting position without resistance, 5 minutes of walking on a flat surface and 10 gentle deep squats. Exactly ninety minutes after the injection, dGEMRIC mapping in the presence of Gd-DTPA²⁻ was performed in the sagittal plane using a single slice inversion recovery fast-spin echo sequence (FOV = 14 cm, matrix 256 x 256, TR = 1800 ms, TE 13 ms, six inversion times (TI) between 50 and 1600 ms, slice thickness 3 mm). The slice positioning was copied from the T2 relaxation time mapping sequence, and the number of the slice in the correct orientation is reduced to one. The remaining slice was then positioned at the centre of the medial and lateral condyles as viewed on the axial scout image. The participants were positioned into an identical position as for the first MRI imaging. Knee with highest degree of OA, as measured by the radiographic Kellgren-Lawrence (K/L) scale, was imaged. In the cases where both knee had identical K/L score the right knee was imaged.

For quality assurance purposes, a set of phantom samples containing certain concentrations of agarose and nickel nitrate to modulate their dGEMRIC and T2 relaxation times were imaged following the study protocol prior to baseline and follow-up measurement sessions, and no evidence of scanner drift was observed during the intervention.

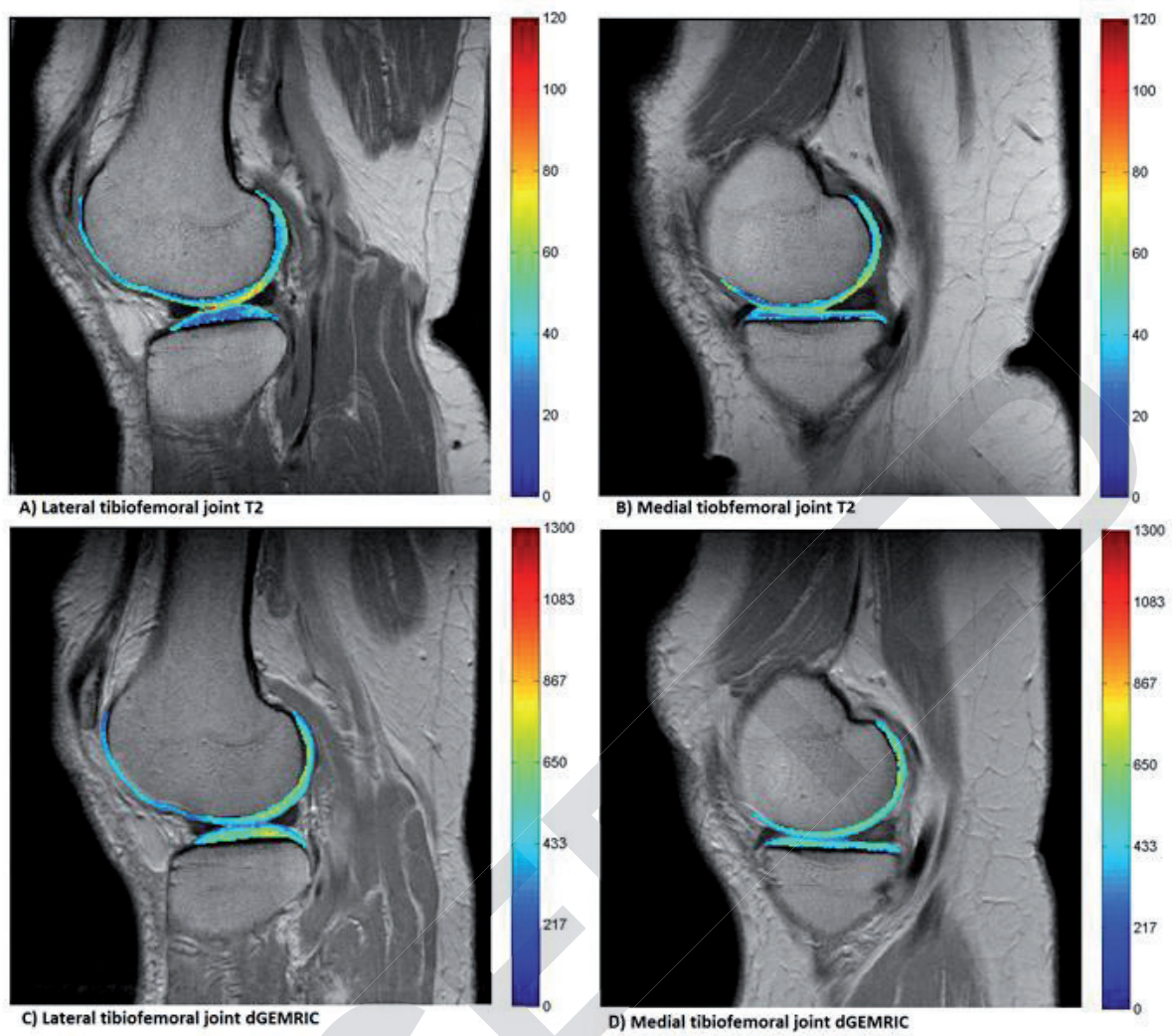


Figure 1. Example image of T2 and dGEMRIC segmentation

Appendix C: Average monthly MET hours in leisure time physical activity tertiles

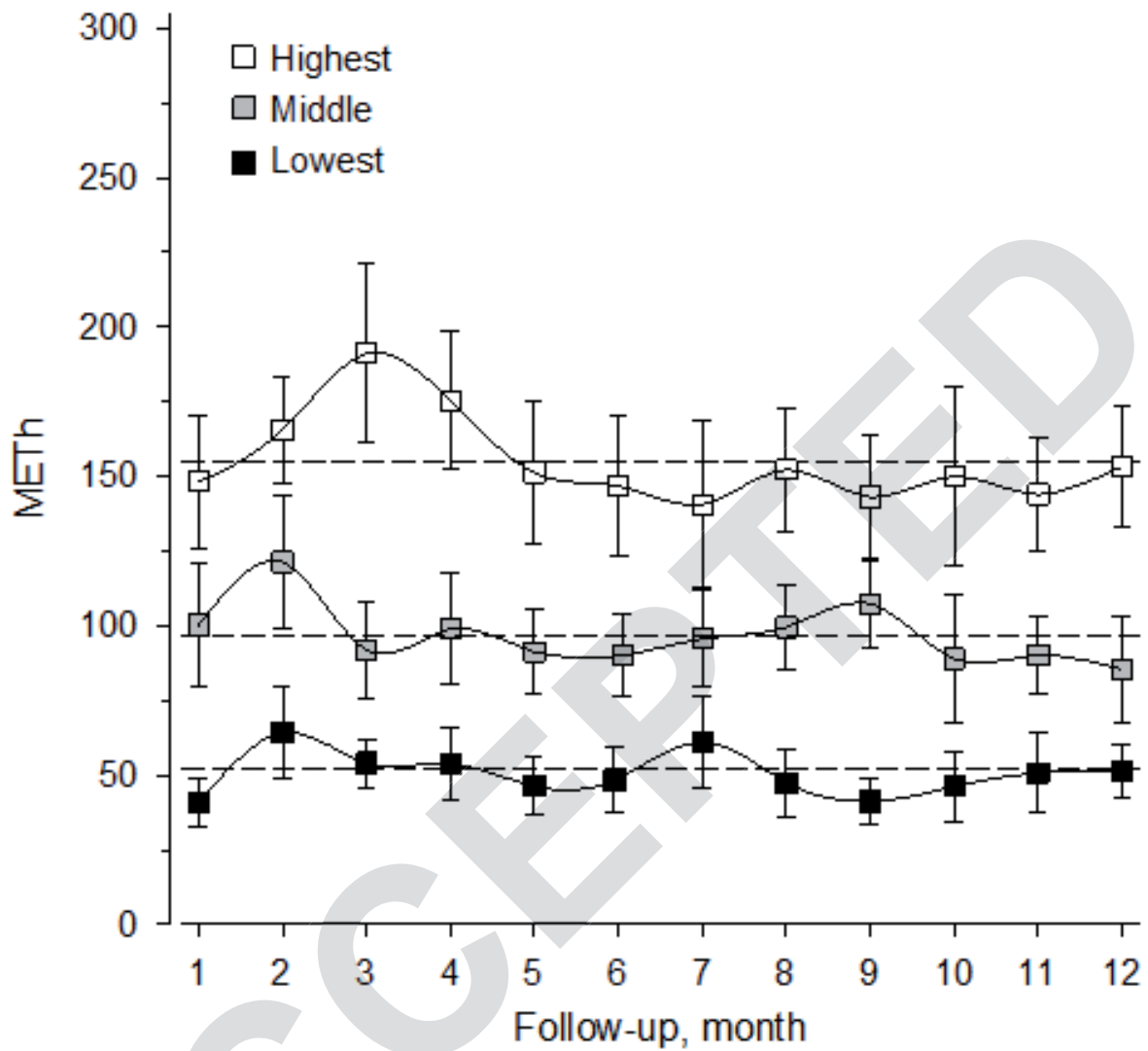


Figure 1. Average monthly MET hours in leisure time physical activity tertiles



IV

RELATIONSHIP BETWEEN LOWER LIMB NEUROMUSCULAR PERFORMANCE AND BONE STRENGTH IN POSTMENOPAUSAL WOMEN WITH MILD KNEE OSTEOARTHRITIS

by

Munukka M, Waller B, Multanen J, Rantalainen T, Häkkinen A, Nieminen M.T,
Lammentausta E, Kujala U.M, Paloneva J, Kautiainen H, Kiviranta I & Heinonen A.
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Relationship between lower limb neuromuscular performance and bone strength in postmenopausal women with mild knee osteoarthritis

M. Munukka¹, B. Waller¹, J. Multanen^{1,2}, T. Rantalainen³, A. Häkkinen^{1,2}, M.T. Nieminen^{4,5,6}, E. Lammentausta^{4,6}, U.M. Kujala¹, J. Paloneva⁷, H. Kautiainen^{8,9,10}, I. Kiviranta¹¹, A. Heinonen¹

¹Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland; ²Department of Physical Medicine and Rehabilitation, Central Finland Central Hospital, Jyväskylä, Finland; ³Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia; ⁴Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland; ⁵Department of Radiology, University of Oulu, Oulu, Finland; ⁶Medical Research Centre, University of Oulu and Oulu University Hospital, Oulu, Finland; ⁷Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland; ⁸Unit of Primary Health Care, Helsinki University Central Hospital, Helsinki, Finland; ⁹Department of General Practice, University of Helsinki, Helsinki, Finland; ¹⁰Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland; ¹¹Department of Orthopaedics and Traumatology, University of Helsinki, and Helsinki University Hospital, Helsinki, Finland

Abstract

Objectives: To investigate whether neuromuscular performance predicts lower limb bone strength in different lower limb sites in postmenopausal women with mild knee osteoarthritis (OA). **Methods:** Neuromuscular performance of 139 volunteer women aged 50-68 with mild knee OA was measured using maximal counter movement jump test, isometric knee flexion and extension force and figure-of-eight-running test. Femoral neck section modulus (Z , mm^3) was determined by data obtained from dual-energy X-ray absorptiometry. Data obtained using peripheral quantitative computed tomography was used to assess distal tibia compressive (BSI_d , g^2/cm^4) and tibial mid-shaft bending ($\text{SSI}_{\text{max, mid}}$, mm^3) strength indices. **Results:** After adjustment for height, weight and age, counter movement jump peak power production was the strongest independent predictor for Z ($\beta=0.44$; $p<0.001$) and for BSI_d ($\beta=0.32$; $p=0.003$). This was also true in concentric net impulse for Z ($\beta=0.37$; $p=0.001$) and for BSI_d ($\beta=0.40$; $p<0.001$). Additionally, knee extension force ($\beta=0.30$; $p<0.001$) and figure-of-eight-running test ($\beta=-0.32$; $p<0.001$) were among strongest independent predictors for BSI_d after adjustments. For $\text{SSI}_{\text{max, mid}}$, concentric net impulse ($\beta=0.33$; $p=0.002$) remained as the strongest independent predictor after adjustments. **Conclusions:** Neuromuscular performance in postmenopausal women with mild knee OA predicted lower limb bone strength in every measured skeletal site.

Keywords: Bone Strength, Neuromuscular Performance, DXA, pQCT, Osteoarthritis

Introduction

Osteoarthritis (OA) and osteoporosis (OP) are universal age-related musculoskeletal disorders that commonly occur in

the same patient population¹⁻³. Degenerative changes in cartilage, e.g. in OA can cause pain and loss of muscle mass and thus the decline in associated force production causes mobility limitations and a decrease in daily physical activity⁴. This results in decreased musculoskeletal loading, causing bone loss⁵. Furthermore, it is relatively well known that bone mineral mass⁶, bone strength and bone structure associate positively with muscle mass⁷. Also, functional decline is contributed to reduction of lean body mass and an increase of fat mass⁸. Reduced muscle strength together with attenuated bone increases the risk for falls and fragility fractures⁹, and represent significant morbidity and healthcare costs^{1,10}.

It has been previously shown that neuromuscular performance is a better indicator of the bone loading environment than

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Corresponding author: Matti Munukka, MSc, Department of Health Sciences, University of Jyväskylä, P.O. Box 35, 40014 Jyväskylä, Finland
E-mail: matti.munukka@jyu.fi

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body mass in models predicting skeletal rigidity in pre- and postmenopausal women¹¹. This notion is supported by previous randomized controlled trials of osteogenic exercise, in which typical osteogenic exercises with high impact loading and fast changes of direction have been shown to have beneficial effects on lower limb bone indices¹²⁻¹⁴. Neuromuscular performance, such as bilateral jumping, is found to be related to tibial strength in young healthy men and women¹⁵. Furthermore, in female athletes, the strong bone structure was found to be attributable to muscle performance in the weight-bearing lower limbs¹⁶. However, high-impact loading may not be most optimal form of exercise for postmenopausal women with mild knee osteoarthritis¹⁷. Thus, it is reasonable and interesting to look at the interplay between neuromuscular characteristics and bone strength to get a better picture how this interaction occurs in postmenopausal women. This interplay should be studied more extensively at several different skeletal sites (femoral neck, tibial mid-shaft and distal tibia) in different population groups, in order to find out new and more relevant information on the potential relationship between exercise related loading and the bone strength. Therefore this study focused on assessing whether neuromuscular performance predicts lower limb bone strength indices in different lower limb sites in postmenopausal women from 50 to 68 years of age with mild knee osteoarthritis.

Methods

Study design and participants

This study was a cross-sectional trial using combined baseline data from two RCTs datasets conducted at Department of Health Sciences in University of Jyväskylä: LuRu (n=52)¹² (ISRCTN58314639) and AquaRehab (n=87)¹⁸ (ISRCTN65346593). In both datasets, postmenopausal women from the Jyväskylä region in Central Finland (total n=621) were recruited on a voluntary basis through local newspaper advertisements. After eligibility was assessed by structured telephone interview, weight bearing radiographs were taken from tibiofemoral joints, dual-energy X-ray absorptiometry (DXA) were taken from both proximal femurs and lumbar spine and clinical examinations were obtained, 139 subjects met the inclusion criteria. According to aforementioned projects, the criteria for eligibility were: volunteer postmenopausal women, between the ages of 50-68 year-old, knee pain on most days, no more than twice a week regular intensive exercise, no illnesses that would limit participation in the exercise interventions or contraindicate exercise, mild tibiofemoral joint OA of grade 1 (possible osteophytes) or 2 (definite osteophytes, possible joint space narrowing) on the radiographic Kellgren/Lawrence (K/L) grading and peripheral quantitative computed tomography (pQCT) measured from the affected knee side (i.e. higher knee K/L side). The criteria for exclusion were: femoral neck bone mineral density (BMD, g/cm²) T-score lower than -2,5 (indicates osteoporosis), body mass index (BMI) ≥ 35 kg/m², surgery of the knee due to trauma or knee instability, inflammatory joint disease, intra-articular

steroid injections in the knee during the previous 12 months, contraindications to MRI and allergies to radiological contrast agents or renal insufficiency. Inclusion criteria in these two RCTs were otherwise similar except for age (LuRu age range: 50-66 years, AquaRehab: 60-68 years) and for BMI (LuRu: ≤ 35 kg/m², AquaRehab: ≤ 34 kg/m²). Measurement protocols were similar in both studies, and description of participant recruitments and outcome measures can be found in detail elsewhere^{12,18}.

Both LuRu –research study protocol (Dnro1E/2008) and AquaRehab –research study protocol (Dnro 19U/2011) were approved by the Ethics Committee of the Central Finland Health Care District. Written informed consent in both studies was obtained from all participants prior to enrolment.

Lower limb bone and body composition measurements

Dual-energy X-ray absorptiometry (DXA). DXA (Lunar Prodigy; GE Lunar Healthcare, Madison, WI, USA) was used to assess rigidity of femoral necks and whole body composition. Proximal femur was scanned with DXA at the narrowest neck section. Femoral neck section modulus (Z, [mm³], an index of bending strength) was calculated with advanced hip structural analysis (AHA) as per manufacturer's software. The femoral neck section modulus (Z) is equal to the cross-sectional moment of inertia (CSMI) divided by the distance from the center of mass to the superior neck margin (y). Coefficient of variation (CV) of femoral neck section modulus (Z) has been assessed to be 5.1% in our laboratory. Total body fat mass and lean mass were analyzed using enCORE software (enCORE 2011, version 13.60.033) for those subjects in AquaRehab study (n=87). *In vivo* precision of these measurements have been reported to be CV of 1.3-2.2%¹⁹.

Peripheral quantitative computed tomography (pQCT). pQCT (XCT 2000, Stratec Medizintechnik GmbH, Pforzheim, Germany) was used to assess the rigidity of the distal and mid-shaft of the tibia from the affected side leg at 5% and 55% of the length of the tibia from the distal end to the mid-shaft of the tibia. A 30 mm planar scout view of the distal tibia was used to define the distal end of tibia. Distal tibia compressive (BSI_d, g²/cm⁴) and tibial mid-shaft bending (SSI_{max}_{mid}, mm³) strength indices were calculated from the data obtained using pQCT. The BSI_d was calculated as:

$$BSI_d = TtD_d^2 * TtAr_d$$

where TtD_d² is the apparent bone density of the total bone cross-section and TtAr_d the total cross-sectional area of the distal tibia. The SSI_{max}_{mid} was calculated as:

$$SSI_{max_{mid}} = \sum_{i=1}^n \frac{y_i^2 * D_i * ar}{1200 * y_{max_{mid}}}$$

where i= index of voxel, D_i= Density of the i:th voxel (in mg/cm³), ar= area of voxel, y_i= distance of the i:th voxel from the bending axis corresponding to the maximal cross-sectional moment of inertia and y_{max}_{mid}= the distance of the most anterior point from the bending axis corresponding to the maximal cross-sectional moment of inertia¹¹.

pQCT bone strength indices predict robustly bone failure in compression at the distal tibia and bending strength at the tibial diaphysis²⁰. CV for the reported pQCT variables has been measured to range from 0.4 to 1.6% in our laboratory¹⁵. DXA and pQCT were measured from the higher K/L grade knee side.

Neuromuscular performance

Counter movement jump test (CMJ). Dynamic maximal muscle power of lower limbs was examined by measuring ground reaction forces in newtons (GRFs, N), peak instantaneous power production during the takeoff phase in watts (W) and concentric net impulse in newton seconds (Ns) with a force platform during counter movement jump test. Subjects were asked to perform a counter movement jump with hands on hips and were instructed to jump as high as possible with the preferred counter movement depth and velocity. The weight of the subject was subtracted from the recorded vertical ground reaction force and then divided by the body mass of the subject to produce vertical acceleration¹¹. A custom made force plate (University of Jyväskylä, Jyväskylä, Finland) was used to assess maximal power traits from the counter movement jump test. Results were analyzed from the vertical ground reaction force using a custom made Matlab script. Maximal power traits were extracted following methodology from our previous study¹¹. Coefficients of variation of 2.5% for jump height²¹ and 3.6% for power²² have been reported in counter movement jump.

Maximal isometric force. Knee extension and flexion force of the affected side leg was measured using an adjustable dynamometer chair (Good strength; Metitur Ltd, Jyväskylä Finland) and recorded in newtons (N). The precision of the tests in our laboratory is 6.3% for the knee extension force and 8.5% for knee flexion force²³.

Figure-of-8-running test. Standardized figure-of-8-running test consisted of two laps around two cones placed 10 meters apart in a figure of eight. Photocells were used to measure time (in seconds) taken to complete the task. The test has been shown to be sensitive (73.5%) and specific (86.1%) for measuring agility and to be effective at detecting decreased motor performance (area under curve 0.86)²⁴.

Health status, general health and mean habitual physical activity (the metabolic equivalent of task, MET hours per week) were assessed by a questionnaire devised by the research group. Self-reported pain, stiffness and physical functional difficulty were assessed by Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire in the range from 0 to 100 mm in the visual analogue scale (VAS)²⁵.

Statistical analyses

The data are presented as means with standard deviations (SD) or as counts with percentages. Linear regression analyses were used to identify the appropriate predictors of the bone strength indices using unadjusted and adjusted (height, weight and age) standardized regression coefficients Beta (β). The Beta value is a measure of how strongly each predictor variable in-

	Mean (SD)
Age (years)	62 (4)
Height (cm)	162 (5)
Body mass (kg)	71 (11)
Body mass index (kg/m ²)	27 (4)
Clinical characteristics	
Kellgren Lawrence grading I/II, n	64/75
Time from menopause (years)	12 (6)
Use of pain killers, n (%)	46 (33)
Glucosamine use occasionally, n (%)	36 (26)
Knee pain during last week (VAS 0-100 mm)	17 (20)
Habitual physical activity (METh/week)	22 (20)
WOMAC pain (VAS 0-100 mm)	11 (11)
WOMAC stiffness (VAS 0-100 mm)	16 (18)
WOMAC physical function (VAS 0-100 mm)	8 (9)
Neuromuscular performance traits	
GRF ^a (N)	135 (24)
Power ^a (W)	1731 (341)
Concentric net impulse ^a (Ns)	108 (19)
Knee extension force (N)	365 (82)
Knee flexion force (N)	174 (50)
Figure-of-8 running (s)	19 (3)
Bone strength indices of the lower limb	
Femoral neck, Z (mm ³)	591 (105)
Tibial mid-shaft, SSI _{max, mid} (mm ³)	1169 (182)
Distal tibia, BSI _d (g ² /cm ⁴)	0.80 (0.19)

GRF = ground reaction force; Power = peak power production; Z = femoral neck section modulus; SSI_{max, mid} = tibial mid-shaft density weighted maximal moment of inertia; BSI_d = distal tibia compressive bone strength index. ^aCalculated from counter movement jump.

Table 1. Descriptive and clinical characteristics of study participants (n=139).

fluences the criterion (dependent) variable. The beta is measured in units of standard deviation. Cohen's standard for Beta values above 0.10, 0.30 and 0.50 represent small, moderate and large relationships, respectively. Hochberg's procedure was used to correct type I error. Statistical comparisons between neuromuscular performance and bone strength indices were made by using t-test or analysis of variance (ANOVA). The bootstrap method was used when the theoretical distribution of the test statistics were unknown or in the case of violation of the assumptions (e.g. non-normality). Correlation coefficients between bone strength indices and body composition were calculated by the Pearson method, using Sidak adjusted probabilities. Stata 13.1, StataCorp LP (College Station, TX, USA) statistical package was used for the analyses.

Results

Table 1 shows the descriptive and clinical characteristics of the study participants. Mean age of the participants was 62 years (range 50 to 68) and BMI 27 kg/m² (range 19 to 35). Mean habitual phys-

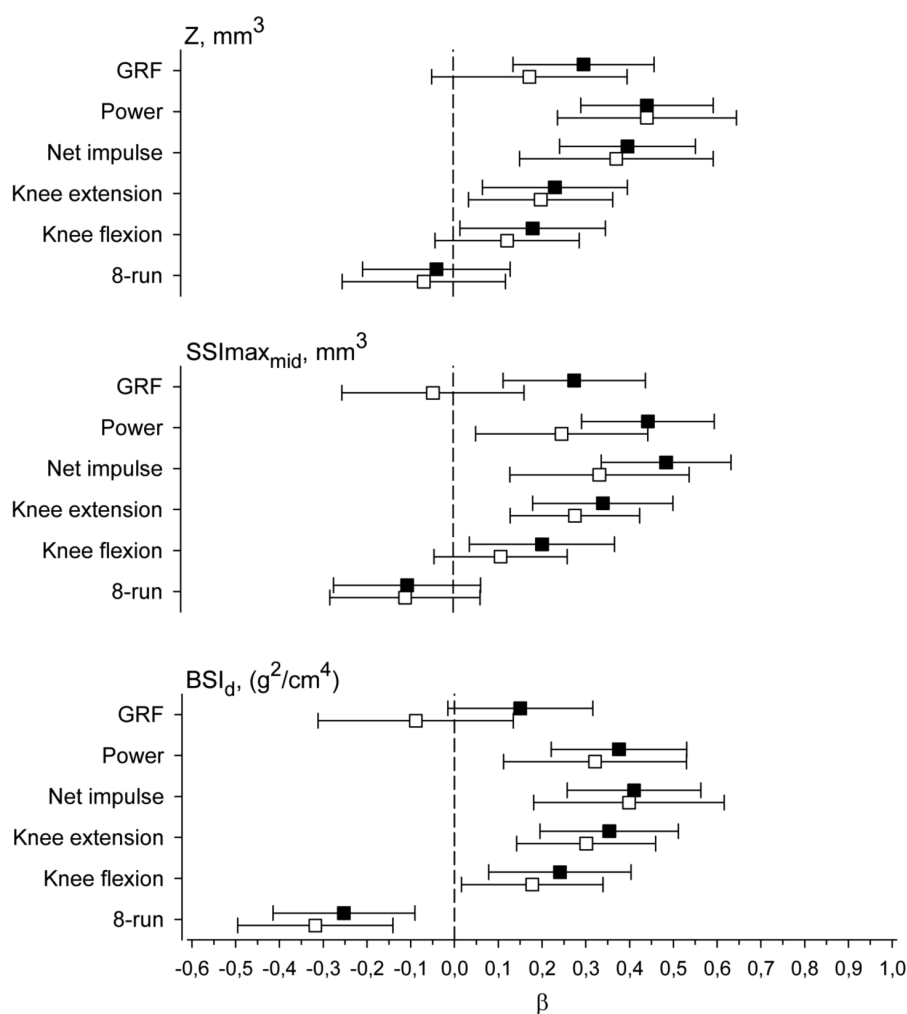


Figure 1. Univariate relationships between exercise related mechanisms and bone strength indices (β -values with 95% confidence intervals). ■= crude and □= height, weight and age adjusted bone strength indices. Z =femoral neck section modulus; $SSImax_{mid}$ =tibial mid-shaft density weighted maximal moment of inertia; BSI_d =distal tibia compressive bone strength index; GRF =ground reaction force; $Power$ =peak power production; $Net\ impulse$ =concentric net impulse; $Knee\ extension$ =knee extension force; $Knee\ flexion$ =knee flexion force; $8-run$ =figure-of-eight-running.

ical activity of the study group was moderate (22 METH/week). Mean (SD) knee pain during last week was 17 mm (20).

Overall, univariate neuromuscular performance variables predicted significantly lower limb bone strength indices (Figure 1). After adjustment for height weight and age, counter movement jump peak power production remained the strongest independent predictor for femoral neck Z ($\beta=0.44$; $p<0.001$) and for distal tibia BSI_d ($\beta=0.32$; $p=0.003$). This was also true in concentric net impulse for femoral neck Z ($\beta=0.37$; $p=0.001$) and for distal tibia BSI_d ($\beta=0.40$; $p<0.001$). Additionally, knee extension force ($\beta=0.30$; $p<0.001$) and figure-of-eight-running test ($\beta=-0.32$; $p<0.001$) were among strongest independent predictors for distal tibia BSI_d after adjustments. In figure-of-eight-running test, faster time (thus negative

value) predicts stronger bone. For tibial mid-shaft $SSImax_{mid}$, concentric net impulse ($\beta=0.33$; $p=0.002$) remained as the strongest independent predictor after adjustments.

Correlation between bone strength indices and body composition is shown in Table 2. In those who had body composition measured ($n=87$), lean mass correlated with all bone strength indices, whereas fat mass did not. After Sidak adjustment, correlation between lean mass and femoral neck Z and tibial mid-shaft $SSImax_{mid}$ remained significant.

Discussion

This study provided new information that neuromuscular performance predicted bone strength along lower limb at femoral

Bone strength indices of the lower limb	Lean mass	Fat mass
Femoral neck, Z (mm ³)	0.32 (0.11 to 0.51)*	0.08 (-0.14 to 0.29)
Tibial mid-shaft, SSI _{max} _{mid} (mm ³)	0.53 (0.37 to 0.66)***	0.17 (-0.06 to 0.39)
Distal tibia, BSI _d (g ² /cm ⁴)	0.22 (0.03 to 0.38)	0.08 (-0.13 to 0.29)

Z= Femoral neck section modulus; SSI_{max}_{mid}= tibial mid-shaft density weighted maximal moment of inertia; BSI_d= distal tibia compressive bone strength index. Sidak adjusted probabilities: * $p < 0.05$, ** $p < 0.001$, *** $p < 0.001$.

Table 2. Correlation coefficients (95% CI) between bone strength indices and body composition.

neck, tibial mid-shaft and distal tibia. Concentric net impulse and peak power production during counter movement jump were the strongest predictors of the lower limb bone strength indices. In addition, knee extension force and figure-of-eight-running were among strongest predictors of bone strength in lower limb. However, figure-of-eight-running (acceleration, deceleration and fast turning during test) time predicted only distal tibia BSI_d. This is in line with the previous findings, which indicate that the highest measurable strain during running occurs at the distal tibia and calcaneus with the greatest strain being generated at the cortex under compression²⁶.

In our study, lower limb concentric net impulse and peak power production, e.g. fast bone loading, predicted lower limb bone strength indices. These findings may mirror the fact that bones adapt their strength through increased strain and stress which are caused by increased loads through forceful muscle contractions⁷. It has been shown, that an 18-month progressive high impact exercise program strengthened the section modulus Z (mean difference 47 mm³, 95% CI: 1 to 92) compared to controls in sedentary premenopausal women⁵. It is known that bone's response to loading is site-specific, and depended on the strain magnitude, rate distribution, strain rate and cycles in the target bone²⁶. Strain rate is shown to be most effective for maximal adaptive bone response in animal experiments²⁷. This is supporting our results, which show that fast and forceful movements are important determinants of lower limb bone strength. When this is translated to human exercise, high impact (e.g. jumping) or odd impact (e.g. squash) exercise loadings with high strain rates and strain magnitudes are reported to be the best way to improve bone strength in femoral neck, distal tibia and tibial mid-shaft^{5,28}.

Furthermore, regular exercise is a promising non-pharmacological method that can prevent the risk of osteoporotic fractures by improving bone quality and preventing falls^{29,30} and it is also recommended treatment for mild knee OA³¹. Despite the fact that high impact loading on regular basis is proposed to be best way to strengthen bones²⁸, typical osteogenic exercises with high-impact loading may not be applicable in postmenopausal women with mild knee OA¹⁷. On the other hand, our recent study indicated that progressively implemented high-impact jumping exercise did not have unfavourable effects on the biochemical properties of the knee cartilage. Further, among postmenopausal women with mild knee OA, impact jumping exercise did not cause knee pain and it had

favourable effects on physical function (e.g. lowered fall risk factors for osteoporotic fractures)¹². Taking into account the results of the present and previous studies^{12,17,28}, lower limb power training, in addition to strength training, could be emphasized in OA and OP training and rehabilitation programs. Nevertheless, cross-sectional study design is not able to demonstrate causal relations; therefore the findings remain purely hypothesis generating.

It has been shown that variation in body mass might not be one of the strongest determinants of skeletal rigidity in lower limbs^{15,32-34} as had been previously proposed^{35,36}. Results of the present study support these findings, showing that neuromuscular performance predicted bone strength indices both in femur and in tibia. Also, in our analysis lean mass correlated significantly with femoral neck Z and tibial mid-shaft SSI_{max}_{mid}, whereas fat mass did not have correlation with bone strength indices. Our observations are in line with a recent study, in which positive correlations was found among lean mass, bone density and bone microstructure in obese adults with metabolic syndrome³⁷. Thus the results highlight the role of exercise and dynamic loading instead of passive loading by body mass in lower limb skeletal rigidity. Variations in fat mass between individuals can potentially double the load the skeleton is required to bear³⁸. In addition to all other unfavourable effects of weight gain, e.g. increased mortality³⁹, it can also aggravate osteoarthritis of the knee in postmenopausal women. Therefore other options instead of weight gain are needed to improve the skeletal properties. Better neuromuscular performance is found to be associated with better skeletal rigidity¹¹ and regular exercise has other beneficial benefits on human body than just weight reduction, such as improved muscle strength, joint range of motion, balance, proprioception and cardiovascular fitness. Thus exercise increases daily physical activity and decreases risk of falling in OA patients⁴⁰. Therefore regular exercise can be recommended as a means to improve skeletal health.

The main strengths of this study were the relatively large subject group and bone strength indices being measured from several locations in the lower limb: femoral neck, tibial mid-shaft and distal tibia. However, knee and distal femur regions were not measured which can be considered as a minor limitation. This study included only 50-68-year-old Caucasian females with mild knee OA recruited as part of the study groups of two larger randomized controlled trials with distinct inclu-

sion/exclusion criteria, and thus results of the present study cannot be generalized to other groups. As aforementioned, cross-sectional design is not able to demonstrate causal relations and as well-known, that limits interpretation of the results.

In conclusion, this study shows that in 50-68 year old postmenopausal women with mild knee OA, neuromuscular performance traits predicted lower limb bone strength in every measured skeletal site. These results provide new and more relevant information when interpreting the effects of neuromuscular performance on bone. This data will help when planning meaningful contents and instructions for bone health related interventions as well as studies among postmenopausal women with mild knee OA.

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References

- Prieto-Alhambra D, Nogues X, Javaid MK, et al. An increased rate of falling leads to a rise in fracture risk in postmenopausal women with self-reported osteoarthritis: a prospective multinational cohort study (GLOW). *Ann Rheum Dis* 2013;72:911-7.
- Blumer MM. Bone mineral content versus bone density in a population with osteoarthritis: a new twist to the controversy? *J Rheumatol* 2005;32:1868-9.
- Bultink IE, Lems WF. Osteoarthritis and osteoporosis: what is the overlap? *Curr Rheumatol Rep* 2013;15:1-8.
- Michael JW, Schlüter-Brust KU, Eysel P. The epidemiology, etiology, diagnosis, and treatment of osteoarthritis of the knee. *Dtsch Arztebl Int* 2010;107:152.
- Heinonen A, Mäntynen J, Kannus P, et al. Effects of High-Impact Training and Detraining on Femoral Neck Structure in Premenopausal Women: A Hip Structural Analysis of an 18-Month Randomized Controlled Exercise Intervention with 3.5-Year Follow-Up. *Physiother Can* 2012;64:98-105.
- Segal NA, Torner JC, Yang M, et al. Muscle mass is more strongly related to hip bone mineral density than is quadriceps strength or lower activity level in adults over age 50 year. *J Clin Densitom* 2008;11:503-10.
- Rantalainen T, Nikander R, Kukuljan S, et al. Mid-femoral and mid-tibial muscle cross-sectional area as predictors of tibial bone strength in middle-aged and older men. *J Musculoskelet Neuronal Interact* 2013;13:273-82.
- Von Stengel S, Kemmler W, Engelke K, et al. Effect of whole-body vibration on neuromuscular performance and body composition for females 65 years and older: a randomized-controlled trial. *Scand J Med Sci Sports* 2012; 22:119-27.
- Karinkanta S, Piirtola M, Sievänen H, et al. Physical therapy approaches to reduce fall and fracture risk among older adults. *Nat Rev Endocrinol* 2010;6:396-407.
- Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *Lancet* 2002;359:1761-7.
- Rantalainen T, Nikander R, Heinonen A, et al. Neuromuscular performance and body mass as indices of bone loading in premenopausal and postmenopausal women. *Bone* 2010;46:964-9.
- Multanen J, Nieminen MT, Hakkinen A, et al. Effects of high-impact training on bone and articular cartilage: 12 months randomized controlled quantitative magnetic resonance imaging study. *J Bone Miner Res* 2014; 29(1):192-201.
- Heinonen A, Mäntynen J, Kannus P, et al. Effects of high-impact training and detraining on femoral neck structure in premenopausal women: a hip structural analysis of an 18-month randomized controlled exercise intervention with 3.5-year follow-up. *Physiother Can* 2012;64:98-105.
- Nikander R, Sievänen H, Heinonen A, et al. Targeted exercise against osteoporosis: a systematic review and meta-analysis for optimising bone strength throughout life. *BMC Med* 2010;8:47.
- Rantalainen T, Heinonen A, Komi PV, et al. Neuromuscular performance and bone structural characteristics in young healthy men and women. *Eur J Appl Physiol* 2008;102:215-22.
- Nikander R, Sievänen H, Uusi-Rasi K, et al. Loading modalities and bone structures at nonweight-bearing upper extremity and weight-bearing lower extremity: a pQCT study of adult female athletes. *Bone* 2006;39:886-94.
- Liikavainio T, Isolehto J, Helminen HJ, et al. Loading and gait symmetry during level and stair walking in asymptomatic subjects with knee osteoarthritis: Importance of quadriceps femoris in reducing impact force during heel strike? *Knee* 2007;14:231-8.
- Waller B, Munukka M, Multanen J, et al. Effects of a progressive aquatic resistance exercise program on the biochemical composition and morphology of cartilage in women with mild knee osteoarthritis: protocol for a randomised controlled trial. *BMC Musculoskelet Disord* 2013;14:82.
- Uusi-Rasi K, Rauhio A, Kannus P, et al. Three-month weight reduction does not compromise bone strength in obese premenopausal women. *Bone* 2010;46:1286-93.
- Kontulainen S, Johnston J, Liu D, et al. Strength indices from pQCT imaging predict up to 85% of variance in bone failure properties at tibial epiphysis and diaphysis. *J Musculoskelet Neuronal Interact* 2008;8:401-9.
- Torvinen S, Kannus P, Sievänen H, et al. Effect of a vibration exposure on muscular performance and body balance. Randomized cross-over study. *Clin Physiol Funct Imaging* 2002;22:145-52.
- Rittweger J, Schiessl H, Felsenberg D, et al. Reproducibility of the jumping mechanography as a test of mechanical power output in physically competent adult and elderly subjects. *J Am Geriatr Soc* 2004;52:128-31.
- Sipilä S, Multanen J, Kallinen M, et al. Effects of strength and endurance training on isometric muscle strength and walking speed in elderly women. *Acta Physiol Scand*

- 1996;156:457-64.
24. Rinne MB, Pasanen ME, Vartiainen MV, et al. Motor performance in physically well-recovered men with traumatic brain injury. *J Rehabil Med* 2006;38:224-9.
 25. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol* 1988;15:1833-40.
 26. Khan K. *Physical activity and bone health*. Champaign, IL: Human Kinetics, 2001.
 27. Lanyon L, Skerry T. Perspective: Postmenopausal Osteoporosis as a Failure of Bone's Adaptation to Functional Loading: A Hypothesis. *J Bone Miner Res* 2001;16:1937-47.
 28. Sievänen H. Bone: Impact loading-nature's way to strengthen bone. *Nat Rev Endocrinol* 2012;8:391-3.
 29. Heinonen A, Kannus P, Sievänen H, et al. Randomised controlled trial of effect of high-impact exercise on selected risk factors for osteoporotic fractures. *Lancet* 1996;348:1343-7.
 30. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database Syst Rev* 2012; 9:CD007146.
 31. Zhang W, Moskowitz R, Nuki G, et al. OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines. *Osteoarthritis Cartilage* 2008;16:137-62.
 32. Beck TJ, Petit MA, Wu G, et al. Does obesity really make the femur stronger? BMD, geometry, and fracture incidence in the women's health initiative-observational study. *J Bone Miner Res* 2009;24:1369-79.
 33. Nikander R, Sievanen H, Uusi-Rasi K, et al. Loading modalities and bone structures at nonweight-bearing upper extremity and weight-bearing lower extremity: a pQCT study of adult female athletes. *Bone* 2006;39:886-94.
 34. Ma H, Leskinen T, Alen M, et al. Long-term leisure time physical activity and properties of bone: a twin study. *J Bone Miner Res* 2009;24:1427-33.
 35. Frost HM. Bone's mechanostat: a 2003 update. *Anat Rec A Discov Mol Cell Evol Biol* 2003;275:1081-101.
 36. Ferretti JL, Cointy GR, Capozza RF, et al. Bone mass, bone strength, muscle-bone interactions, osteopenias and osteoporoses. *Mech Ageing Dev* 2003;124:269-79.
 37. Madeira E, Mafort TT, Madeira M, et al. Lean mass as a predictor of bone density and microarchitecture in adult obese individuals with metabolic syndrome. *Bone* 2014;59:89-92.
 38. Reid I. Relationships between fat and bone. *Osteoporosis Int* 2008;19:595-606.
 39. Flegal KM, Graubard BI, Williamson DF, et al. Excess deaths associated with underweight, overweight, and obesity. *JAMA* 2005;293:1861-7.
 40. Bennell KL, Hinman RS. A review of the clinical evidence for exercise in osteoarthritis of the hip and knee. *J Sci Med Sport* 2011;14:4-9.