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Efficacy of Progressive Aquatic Resistance Training for Tibiofemoral Cartilage in Postmenopausal Women with Mild Knee Osteoarthritis: A Randomised Controlled Trial

Matti Munukka, MSc, Benjamin Waller, MSc, Timo Rantalainen, PhD, Arja Häkkinen, PhD, Miiika T. Nieminen, PhD, Eveliina Lammentausta, PhD, Urho M. Kujala, MD, PhD, Juha Paloneva, MD, PhD, Sarianna Sipilä, PhD, Arttu Peuna, Hannu Kautiainen, BA, Harri Selänne, MD, PhD, Ilkka Kiviranta, MD, PhD, Ari Heinonen, PhD

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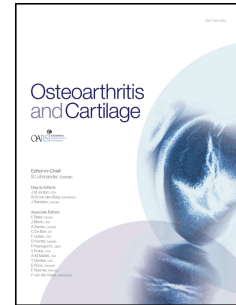
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1 **Efficacy of Progressive Aquatic Resistance Training for Tibiofemoral Cartilage in**
2 **Postmenopausal Women with Mild Knee Osteoarthritis: A Randomised Controlled**
3 **Trial**

4
5 Matti Munukka, MSc^{1*}, Benjamin Waller, MSc^{1*}, Timo Rantalainen, PhD², Arja Häkkinen,
6 PhD^{1,3}, Miika T. Nieminen, PhD^{4,5}, Eveliina Lammentausta, PhD⁴, Urho M. Kujala, MD,
7 PhD¹, Juha Paloneva, MD, PhD⁶, Sarianna Sipilä, PhD^{1,7}, Arttu Peuna^{4,5}, Hannu Kautiainen,
8 BA^{8,9}, Harri Selänne, MD, PhD¹⁰, Ilkka Kiviranta, MD, PhD¹¹, Ari Heinonen, PhD¹

- 9
10 1) Department of Health Sciences, University of Jyväskylä, Jyväskylä, Finland
11 2) Centre for Physical Activity and Nutrition Research, School of Exercise and Nutrition
12 Sciences, Deakin University, Melbourne, Australia
13 3) Department of Physical Medicine and Rehabilitation, Central Finland Central Hospital,
14 Jyväskylä, Finland
15 4) Department of Diagnostic Radiology, Oulu University Hospital, Oulu, Finland
16 5) Centre for Medical Imaging, Physics and Technology research, University of Oulu, Oulu,
17 Finland
18 6) Department of Surgery, Central Finland Central Hospital, Jyväskylä, Finland
19 7) Gerontology Research Center, University of Jyväskylä, Finland
20 8) Department of General Practice and Primary Health Care, University of Helsinki,
21 Helsinki, Finland
22 9) Unit of Primary Health Care, Kuopio University Hospital, Kuopio, Finland
23 10) LIKES Research Centre, Jyväskylä, Finland
24 11) Department of Orthopaedics and Traumatology, University of Helsinki, and Helsinki
25 University Hospital, Helsinki, Finland

26
27 Email addresses:

28 matti.munukka@jyu.fi
29 ben.waller@jyu.fi
30 t.rantalainen@deakin.edu.au
31 arja.hakkinen@jyu.fi
32 miika.nieminen@oulu.fi
33 eveliina.lammentausta@oulu.fi
34 urho.m.kujala@jyu.fi
35 juha.paloneva@ksshp.fi
36 sarianna.sipila@jyu.fi
37 Arttu.Peuna@ppshp.fi
38 hannu.kautiainen@medcare.fi
39 Harri.Selanne@likes.fi
40 ilkka.kiviranta@helsinki.fi
41 ari.o.heinonen@jyu.fi

42
43 *Both authors have equal contribution.

44 Corresponding authors: MSc Matti Munukka and MSc Benjamin Waller. University of
45 Jyväskylä, Department of Health Sciences, P.O. Box 35, FI-40014 University of Jyväskylä,
46 Finland. Phone: +358408053606 and +358408053569. E-mail: matti.munukka@jyu.fi and
47 ben.waller@jyu.fi

48
49 Running title: The impact of aquatic training on tibiofemoral cartilage

50 **Abstract**

51 **Objective:** To study the efficacy of aquatic resistance training on biochemical composition of
52 tibiofemoral cartilage in postmenopausal women with mild knee osteoarthritis (OA). **Design:**
53 87 volunteer postmenopausal women, aged 60-68 years, with mild knee OA (Kellgren
54 Lawrence grades I/II and knee pain) were recruited and randomly assigned to an intervention
55 (n=43) and control (n=44) group. The intervention group participated in 48 supervised
56 aquatic resistance training sessions over 16 weeks while the control group maintained usual
57 level of physical activity. The biochemical composition of the medial and lateral tibiofemoral
58 cartilage was estimated using single-slice transverse relaxation time (T2) mapping and
59 delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC index).
60 Secondary outcomes were cardiorespiratory fitness, isometric knee extension and flexion
61 force and knee injury and osteoarthritis outcome questionnaire. **Results:** After 4-months
62 aquatic training, there was a significant decrease in both T2 -1.2ms (95% CI: -2.3 to -0.1,
63 $p=0.021$) and dGEMRIC index -23ms (-43 to -3, $p=0.016$) in the training group compared to
64 controls in the full thickness posterior region of interest (ROI) of the medial femoral
65 cartilage. Cardiorespiratory fitness significantly improved in the intervention group by 9.8%
66 ($p=0.010$). **Conclusions:** Our results suggest that, in postmenopausal women with mild knee
67 OA, the integrity of the collagen-interstitial water environment (T2) of the tibiofemoral
68 cartilage may be responsive to low shear and compressive forces during aquatic resistance
69 training. More research is required to understand the exact nature of acute responses in
70 dGEMRIC index to this type of loading. Further, aquatic resistance training improves
71 cardiorespiratory fitness.

72 **Keywords:** Osteoarthritis; Aquatic Exercise; Magnetic Resonance Imaging (MRI), Cartilage,
73 Randomised Controlled Trial

74 **Trial registration number:** ISRCTN65346593

75 INTRODUCTION

76

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

86

87 There is no known cure or treatment that prevents or reverses the biochemical changes in the
88 cartilage, therefore, the current management of OA focuses on reducing the symptoms and
89 decreased function associated with the disease¹. Exercise, irrespective of modality (land or
90 water) or type (strength or aerobic), has been shown to be effective in achieving these aims^{5,6}.
91 Moreover, an active life style with participation in exercise has been shown to be beneficial
92 for maintenance of the biochemical properties of cartilage in both animals^{7,8} and humans^{9,10}.
93 Further, exercise has been shown to reverse cartilage atrophy seen in disuse and
94 immobilisation studies^{11,12} and slow down progression of OA in animals¹³. Therefore,
95 exercise could be an effective intervention for the maintenance of cartilage health. However,
96 studies investigating the effect of exercise interventions on healthy and degenerated human
97 cartilage are sparse¹⁴⁻¹⁷. Only two previous studies have investigated the effects of land based
98 exercise on the biochemical composition of cartilage in postmenopausal women with mild
99 knee OA, i.e. Kellgren-Lawrence grades I/II and knee pain^{15,16}. We found an improvement in

100 the collagen matrix in the patella cartilage of women with mild knee OA following a one-
101 year, three time a week, high-impact exercise intervention¹⁵ while we did not see any
102 worsening or improvement in the collagen matrix or GAG concentration of the tibiofemoral
103 cartilage in the same study¹⁶. Therefore, there is sufficient evidence to show cartilage health
104 is maintained by appropriate mechanical stimulus and environment^{9,18}.

105

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

118 MATERIALS AND METHODS

119

120 Study design

121

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

132

133 Subject recruitment

134

135 A multistage recruitment process was implemented (Figure 1). Initially, postmenopausal
136 women from the Jyväskylä region in Central Finland were voluntarily recruited through
137 advertisements in local newspapers. Preliminary eligibility was assessed using a structured
138 telephone interview (n=323), followed by evaluation of osteoarthritis severity in the
139 tibiofemoral joint with radiographs (n=180) and finally through medical screening (n=111).
140 Inclusion criteria were: postmenopausal woman aged 60–68 years, experiencing knee pain on
141 most days, participates in intensive exercise \leq twice a week, radiographic changes in

142 tibiofemoral joint K/L I or II, no previous cancer or chemotherapy, no medical
143 contraindications or other limitations to full participation in an intensive aquatic training
144 program and complete T2 data. Exclusion criteria included a T-score <-2.5 (indicating
145 osteoporosis)²⁵ measured from the femoral neck using dual-energy X-ray absorptiometry
146 (DXA), resting knee pain visual analogue scale (VAS) $>50/100$, surgery of the knee due to
147 trauma or knee instability, meniscectomy within the last 12 months, inflammatory joint
148 disease, intra-articular steroid injections in the knee during the previous 12 months,
149 contraindications to MRI and allergies to contrast agents or renal insufficiency. Due to
150 confounding factors related to obesity, a body mass index (BMI) of $>34 \text{ kg/m}^2$ was an
151 exclusion criterion.

152

153

Figure 1 here.

154

155 **Randomisation and blinding**

156

157 After baseline measurements, all participants were randomly allocated with a three digit
158 identification number (ID) to blind researchers to intervention allocation and provision. A
159 blinded statistician, only provided with ID and K/L grade, performed a computer generated
160 block randomisation of size of 10, stratified according to K/L grade I or II. The MRIs were
161 performed by external radiographers and segmentation was performed blinded to intervention
162 allocation.

163

164

165 **Health questionnaire**

166

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

172

173 **Primary outcome measures**

174

175 Primary outcomes for this study were T2 relaxation time (T2) mapping (milliseconds, ms)
176 and delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC
177 index, ms). Images were taken using a Siemens Magnetom Symphony Quantum 1.5-T
178 scanner (Siemens AG, Medical Solutions, Erlangen, Germany). Single sagittal slice images
179 from the centre of the medial and lateral femoral condyles were taken from the knee with the
180 highest K/L grade (affected knee). In cases of identical grading bilaterally, the right knee was
181 imaged. Images were manually segmented using an in-house MATLAB application with
182 built-in motion correction for dGEMRIC (Mathworks, Inc. Natick, MA, USA). In this study
183 we divided the femoral cartilage into three ROIs; anterior, central and posterior (Figure 2).
184 dGEMRIC indices were corrected for BMI²⁷. Precision, scan-rescan, (CV_{RMS}) of dGEMRIC
185 in asymptomatic subjects is 7% for full-thickness ROIs and 5% for bulk cartilage²⁸. In our
186 laboratory, the inter-observer error (CV_{RMS}) for T2 full-thickness ROIs was 1.3% to 3.3%
187 and 2.8% to 4.0% for dGEMRIC index. The full MRI protocol and example images are
188 provided in the online supplemental material.

189

190

Figure 2 here.

191

192 **Secondary outcomes**

193

194 **Physical performance**

195

196 Cardiorespiratory fitness (VO₂ peak, ml/kg/min) was estimated using the UKK 2 km walking
197 test (UKK Institute, Tampere, Finland)²⁹. Isometric knee extension and flexion force (N) of
198 the affected knee was measured using an adjustable dynamometer chair (Good strength;
199 Metitur Ltd, Jyväskylä, Finland)³⁰.

200

201 **Self-reported symptoms**

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

207

208 **Daily physical activity**

209

210 Daily physical activity, for the whole intervention period, of each participant was recorded
211 using a leisure time physical activity diary from which metabolic equivalent task (MET-

212 hours) per week was calculated²⁶. In week 13 of the intervention period the daily physical
213 activity (excluding intervention) was measured for 3 consecutive days including one weekend
214 day using an accelerometer (Hookie AM 20, Traxmeet Finland). Mean amplitude deviation
215 (MAD) of the resultant acceleration signal for each 5-sec epoch were calculated and
216 categorized according to Vähä-Ypyä *et al.*³³.

217

218 **Exercise protocol**

219

220 The participants in the intervention group received one hour of supervised lower limb aquatic
221 resistance training three times a week for 16 weeks, for a total of 48 training sessions.

222 Resistance of exercises was progressed with three different levels: barefoot, small fins and
223 large resistance boots²¹ and the training leg performed all the movements without contact
224 with the pool walls or bottom i.e. non-weight bearing. The intervention was completed in
225 small groups of 6-8 subjects in a pool heated to 30-32 degrees with two instructors: one
226 ensuring intensity and the other full range of movement. Intensity of the training sessions was
227 set at “as hard and fast as possible” to ensure maximal muscle contraction. Pöyhönen *et al.*³⁴
228 discovered that during maximal knee flexion and extension exercises in water with large
229 resistance boots the drag forces produced were 80-85% (145 ± 30 N) of maximal isokinetic
230 movements. Full range of motion was strictly controlled for to ensure optimal movement of
231 synovial fluid and exposure of the whole cartilage to the low compressive and shear forces
232 created by the muscle contraction and movement. Training intensity was monitored using
233 heart rate monitors (Polar Electro Ltd, Kempele, Finland), rate of perceived exertion (RPE)
234 using the Borg 6-20 scale³⁵ and number of repetitions achieved per movement. Full

235 description of exercises and training methodology can be found from the online supplemental
236 material.

237

238 **Control group**

239

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

243

244 **Statistical analyses**

245

246 The main outcome variables were analysed according to the intention-to-treat analysis
247 principle. Changes in all outcomes were analysed using the bootstrap type analysis of
248 covariance (ANCOVA); confidence interval were obtained by bias-corrected bootstrapping
249 (5000 replications) due to violation of distributions assumptions. T2 was adjusted for baseline
250 value, height and weight and dGEMRIC index was adjusted for baseline value only.

251 Secondary outcomes were adjusted for baseline value. There are multiple endpoints in this
252 study, and results have to be viewed with certain provisos. All p-values and confidence
253 intervals are quoted, rather than introducing the problems and potential errors associated with
254 formal adjustments for potential multiplicity issues. Between-group changes in all outcomes
255 are reported in text as mean difference (95% confidence interval, adjusted p-value). Effect
256 size (d) was calculated by using the method of Cohen³⁶ where an effect size of 0.20 is
257 considered small, 0.50 moderate, and 0.80 large. Confidence intervals for the effect sizes

258 were obtained by bias-corrected bootstrapping (5000 replications). Statistical analyses were
259 performed using statistical software (Stata, release 13.1, StataCorp, College Station, Texas).

260

261 Target sample size of 70 (35 per research arm) was required to ensure the power of at least
262 80% to detect a difference of 40 ms effect in dGEMRIC between the groups at two-side
263 $\alpha=0.05$. Predicting a dropout rate of about 10% we aimed to recruit at least 80 participants at
264 baseline.

265 RESULTS

266

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

270

271

Table 1 here.

272

273 Program Feasibility

274

275 Drop-out rate, during the 4-month intervention period, for each group was 2.3% (n=1 per
276 group) (Figure 1). Training compliance was 88% and mean (SD) training frequency was 2.6
277 (0.5) per week (including dropouts). The average intensity of each training session was RPE
278 15 (range, 12-17) and average (SD) maximum heart rate was 144 (12) beats per minute. The
279 mean (SD) number of repetitions completed per session with the affected leg was 481 (67),
280 416 (68) and 387 (58) for barefoot, small fins and large boots, respectively. 70.5% of these
281 repetitions involved full knee active extension and flexion which was mean 134.4 (SD, 5.6)
282 degrees (affected knee) as measured during baseline assessment.

283

284 Harms

285

286 There were 2 medical consultations (bilateral knee pain and dyspnoea) as a result of the
287 aquatic training. One subject from the control group required a medical consultation for knee
288 pain after the baseline physical performance measures. All three subjects continued their
289 participation in the study and attended follow-up measurements.

290

291 **Primary outcomes**

292

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

301

302 T2 and dGEMRIC index baseline values, changes, group differences and effect sizes
303 (Cohen's *d*) at the end of the 4-month intervention are given in table 2. There was a
304 significant decrease in both T2, mean difference -1.2ms (95% CI: -2.2 to -0.2, $p=0.021$) and
305 dGEMRIC index -23ms (-43 to -3, $p=0.022$) in the training group compared to controls in the
306 full thickness posterior ROI of the medial femoral cartilage. Further, significant decreases in
307 the training group compared to controls were only seen in the deep posterior and not
308 superficial ROI of the medial femoral cartilage, -1.6ms (-3.0 to -0.3, $p=0.016$), and -26ms (-
309 50 to -3, $p=0.030$), for T2 and dGEMRIC index respectively (Figure 3). Values for the deep
310 and superficial posterior ROI (Figure 3) can be found from the online supplemental material.

311

312

Table 2 here.

313

314

Figure 3 here.

315

316 **Secondary outcomes**

317

318 Cardiorespiratory fitness VO_2 peak increased 9.8% in the training group and 4.4% in the
319 control group ($d=0.58$, $p=0.010$). There were no between group differences in the knee
320 extension or flexion muscle force or in any domains of KOOS (Table 3).

321

322

Table 3 here.

323

324 **Daily physical activity**

325

326 The total mean (SD) MET-hours per week, including the intervention, were 40 (13) and 26
327 (16) in the training and control group respectively ($p<0.001$). No between group differences
328 were seen in MET activity once the intervention activity was removed ($p=0.112$). There was
329 no significant difference between the groups in physical activity as measured with
330 accelerometers, excluding the intervention. Sedentary behavior accounted for 80% (5.0) or
331 13,903 (869) MADs of daily activity. The remaining physical activity was divided into slow
332 walking 3166 (821), normal walking 198 (175) and brisk walking jogging and running
333 together 1.7 (1.4) MADs.

334 **DISCUSSION**

335

336 As far as we know, this is the first study to show a response in the biochemical composition
337 of tibiofemoral cartilage following 4-months of progressive aquatic resistance training in
338 postmenopausal women with mild knee OA. A small significant change was observed in the
339 biochemical composition of the medial posterior femoral cartilage, which is less loaded
340 during activities of daily living³⁷. Additionally, the training significantly improved
341 cardiorespiratory capacity but had no significant effect on muscle force and self-reported
342 symptoms.

343

344 This is the first study to show concurrent changes in both T2 and dGEMRIC index in an
345 exercise intervention study. However, both MRI techniques have only been previously
346 implemented once in the same study. In the study by Multanen *et al.*¹⁶ we investigated the
347 effects of a land-based impact intervention on the biochemical composition tibiofemoral
348 cartilage in postmenopausal women with mild knee OA. No positive or negative effect was
349 observed with either MRI technique, however, the posterior ROIs were not reported. In this
350 study¹⁶ the degree of knee motion during the land-based intervention was 0-65 degree and
351 therefore the posterior ROI was not directly loaded. Knee flexion of over 90 degrees is
352 required to produce contact between the posterior ROI of the femur and central tibia³⁸ which
353 was achieved with our intervention at high frequency. Therefore, our results suggest that the
354 chondrocytes in the posterior region of the femoral cartilage in persons with mild knee OA
355 may have a lower threshold for adaption compared to the central and might be more
356 responsive to the high repetition low shear and compressive cyclic forces produced in the
357 aquatic resistance training. In contrast, the chondrocytes in the central region of the femur
358 and tibia cartilage may require a higher or atypical load to stimulate an adaptive response.

359 Further, the response was limited to the medial femoral cartilage possibly due to anatomical
360 differences. The medial tibial plateau is concave compared to the convex surface of the
361 lateral side, thus on the medial tibiofemoral joint there is greater contact between the cartilage
362 surfaces³⁹.

363

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

376

377 We found a corresponding significant decrease in dGEMRIC index in the posterior region of
378 medial femoral cartilage and again more specifically in its deep region. A lower dGEMRIC
379 index is associated with a lower GAG concentration, thus, a decrease in dGEMRIC index
380 may indicate degeneration of cartilage^{42,43}. Our results suggest that the aquatic resistance
381 training may have produced a decrease in GAG concentration within the cartilage matrix or
382 faster contrast agent diffusion in to the cartilage through increased permeability of the
383 cartilage surface⁴⁴. These are characteristics of OA progression⁴. These results conflict with

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

402

403 In line with the findings of our recent systematic review⁶, we did not see a significant change
404 in muscle force. However, we used isometric muscle testing whereas, the muscle contraction
405 during isokinetic strength testing mimics closer the true muscle work performed during
406 aquatic resistance training and could have been more sensitive to change. The improvements
407 in cardiorespiratory fitness are in line with other studies investigating the effects of aerobic
408 aquatic training⁴⁷. An aquatic exercise program which also includes neuromuscular exercises

409 e.g. partial weight bearing exercises might produce better improvements in neuromuscular
410 performance and possibly stimulate GAG production¹⁴ as it is possible to speculate that the
411 loading mechanics in our study may have been ineffective for this purpose. There were no
412 between group changes in any of the domains of the KOOS, this lack of significance is not a
413 surprise given the high values reported at baseline. In combination with the results from the
414 measures of physical performance and KOOS there is no indication that aquatic exercises had
415 a harmful effect on clinical findings in this population. Therefore, aquatic resistance training
416 of sufficient intensity to improve cardiorespiratory function is well tolerated, has high
417 compliance and does not increase pain in women with mild knee OA. Further research should
418 focus on the efficacy of aquatic resistance training for people with more severe stages of OA
419 progression.

420

421 The strengths of this study include the high adherence to a highly intensive aquatic training
422 program. This study fulfilled all the important quality criteria of an RCT, except for blinding
423 the participants to exercise therapy, which is common in exercise therapy studies⁴⁸. Strict
424 imaging procedure and segmentation rules ensured good stability and repeatability of the T2
425 and dGEMRIC indices. This limits, but does not rule out, the possibility that the results of
426 this study are affected by the magic angle (particularly T2) and partial volume effects. The
427 long imaging time in dGEMRIC mapping might result in motion artefact which was
428 controlled for in our study by using a motion correction technique built into the in-house
429 software, as well as strict inclusion/exclusion criteria for image quality. Minor limitations
430 include: MRI imaging performed with a 1.5 tesla scanner, whereas a 3.0 tesla scanner would
431 have produced better spatial resolution and higher signal-to-noise ratio. The mean changes
432 seen in T2 and dGEMRIC index fall within the upper limits of our measurement error for
433 both techniques therefore we cannot exclude measurement error as a possible explanation for

434 our findings. Further, this study had multiple endpoints and therefore results have to be
435 viewed with caution. In some cases, occasionally thinned and deteriorated cartilage and
436 movement or pulsating artery artefact prevented reliable segmentation of cartilage resulting
437 in lost data. Also, we used single-slice segmenting method assessing articular cartilage,
438 whereas multi-slice method might have produced more a comprehensive view of the knee
439 cartilage. The MRI analysis application divided cartilage to deep and superficial
440 compartments (50%/50%) and due to the 1.5T scanner used, segmented cartilage thickness
441 was from two to five voxels reducing the spatial accuracy and therefore care should be taken
442 when interpreting these results. Pre-contrast T1 imaging was not used in this study however
443 its importance has been questioned and it is felt this omission does not affect our
444 conclusions^{46,49}. Classification of OA severity was performed using a combination of pain
445 and Kellgren-Lawrence classification (weight-bearing) and therefore it was not possible to
446 differentiate between healthy and biomechanically altered cartilage between ROIs and
447 condyles⁵⁰. It is still unknown if an aquatic training program of longer than 4-months would
448 have created a global response throughout the cartilage. It is plausible to hypothesise that as
449 cartilage health in one ROI improves it may cause a positive response in adjacent ROI's. Due
450 to the strict inclusion criteria, our results cannot be directly applied to people with later stage
451 OA, older or obese women and men. Finally, the authors acknowledge that the different
452 qMRI parameters and their interactions are not yet fully understood and further investigations
453 about the interaction between exercise and these parameters are warranted.

454

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

459 loading. Clinical relevance of our findings remains unclear but strongly warrants further
460 research. Additionally, aquatic resistance training of sufficient intensity to improve
461 cardiorespiratory function is well tolerated, has high compliance and low risk of harm
462 amongst women with mild knee OA.

463

464 **Author contributions**

465

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

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

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

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

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

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

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

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

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

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

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

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

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

501 Heinonen, Ari: Conception and design, analysis and interpretation of the data, drafting of the
502 article, critical revision of the article for important intellectual content, final approval of the
503 article, obtaining of funding.

504

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512

513 **Conflict of interest**

514

515 There is no conflict of interest for any authors.

516

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- 659

660 **Tables**

661

662 **Table 1.** 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, <i>n</i> (%) of users	11 (25.6)	9 (20.5)
Glucosamine use occasionally, <i>n</i> (%)	12 (28)	8 (18)
Kellgren Lawrence grade, <i>n</i> (%)		
Grade 1	23 (53.5)	24 (54.5)
Grade 2	20 (46.5)	20 (45.5)
Knee pain during last week, (VAS, mm) ^a		
• Affected leg	28 (25)	24 (19)
• Non-affected leg	24 (19)	23 (18)
Habitual physical activity (MET _h /week)	29 (31)	36 (33)

663 Values are means (SD) or *n* (%)664 MET_h = metabolic equivalent task hour.665 ^a Range, 0-100 mm

666 **Table 2.** Effects of aquatic training on T2 relaxation time and dGEMRIC index in full-thickness ROIs.
 667

	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 ^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	0.30 ^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	0.47 ^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	0.021 ^a
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 ^a
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 ^a
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 ^b
Posterior	422 (60)	428 (57)	2 (-10 to 16)	6 (-8 to 22)	0.08 (-0.40 to 0.57)	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	0.13 ^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 ^b
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 ^b
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 ^b

668

669 T2 = transverse relaxation time; ^aANCOVA: adjusted for baseline value, height and weight.
670 dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage; ^bANCOVA: adjusted for baseline value.
671 In T2 low values correspond to improved integrity and orientation of the collagen fibres and a decrease in hydration of articular cartilage.
672 In dGEMRIC, high values correspond to high glycosaminoglycan concentration.
673 *Missing data for dGEMRIC [†]n=16, [§]n=12

674 **Table 3.** Effects of aquatic training on physical performance and clinical symptoms

675

	Baseline, mean (SD)		Change to month 4, mean (95% CI)		Effect Size (95% CI)	P-value	
	Training	Controls	Training	Controls		Crude	Adjusted ^a
	(n=42)	(n=42)	(n=42)	(n=42)			
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

676

677 ADL= activities of daily living; Sport = sports and recreation; QOL = knee related quality of life, KOOS = Knee injury and osteoarthritis
678 outcome score
679 ^aANCOVA: adjusted for baseline

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680 **FIGURE LEGENDS**

681

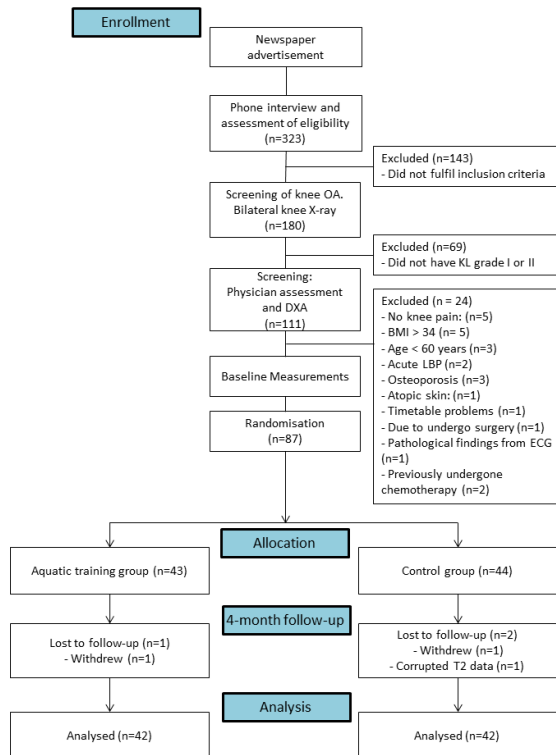
682 **Figure 1.** Flow chart showing enrolment, allocation and four month end measurements.

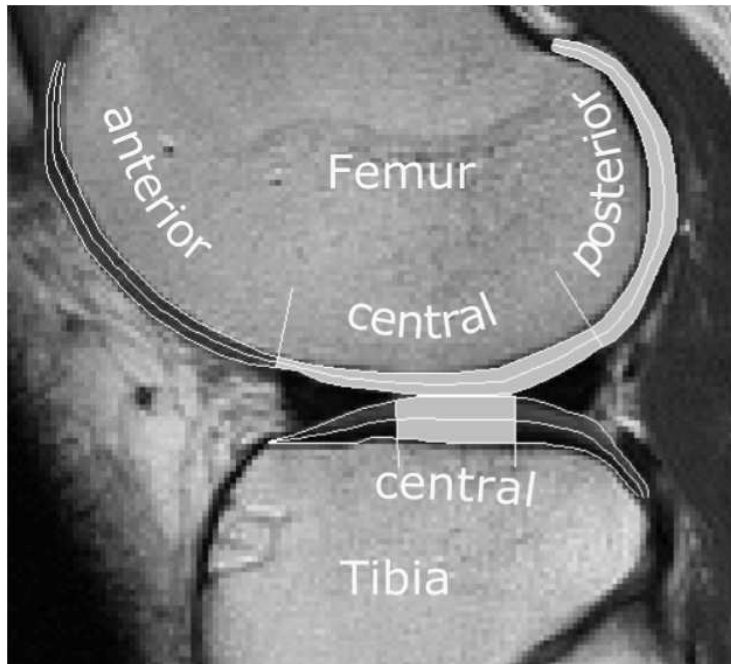
683

684 **Figure 2.** Illustration of the region of interests (ROIs) in the full-thickness femoral and tibial
685 cartilage. Midlines split both femoral and tibial cartilage into superficial and deep sections.

686

687 **Figure 3.** Magnitude of effect (Cohen's d and 95% CI) at superficial and deep layers of T2
688 and dGEMRIC cartilage ROIs from medial and lateral condyles. T2 = transverse relaxation
689 time; dGEMRIC = delayed gadolinium-enhanced magnetic resonance imaging of cartilage;
690 sPF = superficial posterior femur; dPF = deep posterior femur.





ACCEPTED MANUSCRIPT

