484

EFFECT OF INITIATION TIMING OF GENTLE TREADMILL EXERCISE ON CARTILAGE AND SUBCHONDRAL BONE IN A MODEL OF DESTABILIZATION OF MEDIAL MENISCUS OF RATS


Purpose: Knee osteoarthritis (OA) is considered a multifactorial whole-joint disease which includes articular cartilage degeneration and subchondral bone damage. As we showed previously, cartilage degeneration and subchondral bone porosity were confirmed in 4 weeks after destabilization of medial meniscus (DMM) surgery which should be treated to prevent further progression of knee OA (Iijima H et al. Osteoarthritis Cartilage 2014). Mechanical loading such as treadmill exercise may be one of the important factor, which regulates the maintenance of both cartilage and subchondral bone of OA. However, there were few study which investigates effect of treadmill exercise focusing on initiation timing of exercise. The present study was undertaken to examine the effect of treadmill exercise timing on cartilage and subchondral bone in an experimental rat model of DMM.

Methods: All experiments were performed according to the protocol approved by the Animal Care and Use Committee of Kyoto University. Twelve-week-old male Wistar rats (n = 32) underwent DMM surgery in their right knee and sham surgery in their left knee. As shown in Figure 1, the rats were assigned to DMM, DMM + walk (0-4w), DMM + walk (4-8w) and DMM + walk (0-8w) groups (n = 8/group). Animals in DMM + walk (0-4w), DMM + walk (4-8w) and DMM + walk (0-8w) groups were subjected to treadmill exercise from day 2 through week 4, week 4 through week 8 and day 2 through week 8 after surgery respectively, which was walking for 12 m/min, 30 min/day, 5 days/ week. Animals in the DMM group were allowed to move freely in standardized cages without any treadmill exercise for 8 weeks. Cartilage and subchondral bone changes were evaluated by histological and μ-CT analysis, respectively.

Results: In the DMM knee of all experimental groups, osteoclast-created subchondral bone cysts (SBCs) were confirmed by TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity.

Conclusions: These results indicate biomechanical and biological association between degenerated cartilage and damaged subchondral bone which may exaggerate cartilage degeneration. Interestingly, 4-week exercise intervention started 4 weeks after DMM surgery prevented cartilage degeneration and subchondral bone damage compared with that started day 2 for 4-week, indicating that the initiation of treadmill exercise may be an important factor to determine its effectiveness. Further study is needed to clarify the mechanism of these differences due to initiation timing of exercise on cartilage and subchondral bone.

485

CHARACTERIZATION OF THE MATRIX DRIVEN OSTEOCLAST SUBTYPE IN OSTEOARTHRITIS


Purpose: Osteoarthritis is a heterogenous disease of the entire joint, involving bone, cartilage and synovial inflammation. Subchondral bone sclerosis is well-documented in OA which support a key role for osteoclastic mediated bone remodeling in the subchondral bone compartment, i.e. in the generation of bone marrow lesions (BMLs) albeit the molecular details remain to be discovered. Normal cortical bone is replaced on average every 25 years, whereas trabecular bone is replaced 4 times as fast. The subchondral bone remodeling has been reported to be as much as 20 fold elevated compared to normal bone. Consequently the bone composition of subchondral bone, and the phenotype of osteoclasts associated with that may be altered.

To investigate the qualitative response of osteoclasts to different types of bone, (newly formed bone, aged bone or subchondral bone) we developed an in vitro system for investigating the phenotype of human osteoclasts on different bone types and ages.

Methods: To assess effects of matrix on osteoclastogenesis, CD14 positive human monocytes were seeded on either either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity. For effects of matrix on bone resorption, mature human CD14-mono- cyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calciﬁed cartilage) or articular cartilage, and cultured for 14 days to allow osteoclasts to form. Osteoclastogenesis was assessed using TRACP activity.

Results: On aged bone, the osteoclasts showed markedly higher resorptive activity than on young bone, a finding which was caused by increased osteoclastogenesis, evident by a 400% increase in osteoclast number (TRACP) and 150% increase in bone resorption (CTX-I), (p<0.01). Interestingly, on subchondral bone and articular cartilage a switch toward a more MMP driven resorption subtype was observed.

Conclusions: Osteoclasts on young remodeled bone resorbed signiﬁcant less than osteoclasts on aged bone. This osteoclast phenotype may reﬂect the phenotype of subchondral osteoclasts and contribute signiﬁcantly to the sclerotic bone phenotype of OA patients.

486

T1p AND T2 MAPPING MRI SHOW NO DIFFERENCE IN CARTILAGE COMPOSITION BETWEEN PATIENTS WITH PATELLOFEMORAL PAIN AND HEALTHY CONTROL SUBJECTS


Purpose: Patellofemoral pain (PFP) is a common knee condition, especially occurring among young and physically active individuals. A variety of treatments, such as exercise therapy and orthoses, are applied, but effects are small and a substantial group of patients with persistent complaints remains. It has been suggested that PFP may be a precursor to patellofemoral osteoarthritis (POFA), however the evidence is weak. Since PFP involves a young patient population, it could be hypothesized that the content of the cartilage might play an
important role in the etiology of PFP. It has been suggested that a change in cartilage composition, due to deterioration of structural components like collagen and glycosaminoglycan’s (GAGs), precedes morphological characteristics of cartilage damage in OA patients. With innovative MRI sequences, including T1p and T2 mapping, it is possible to measure these early changes in cartilage composition quantitatively by measuring cartilage content. Therefore, the purpose of this study was to investigate differences in cartilage composition between patients with PFP and control subjects using quantitative T1p and T2 mapping MRI.

Methods: Patients diagnosed with PFP and healthy control subjects aged 14-40 years were included in a cross-sectional case-control study. Measures included a questionnaire, physical examination and MRI at 3T. MRI comprised morphologic, T1p and T2 mapping sequences. T1p and T2 mapping sequences were conducted to measure cartilage glycosaminoglycan and collagen content, respectively. In-house developed software was used for image post-processing in order to calculate T1p and T2 relaxation times (see Figure 1). Higher relaxation times equal less content and less content equals a lower cartilage quality. Differences in T1p and T2 relaxation times for trochlear and patellar cartilage were compared between patients and control subjects by linear regression analyses, adjusted for potential confounders.

Results: 59 patients and 67 control subjects were included. BMI was significantly lower and sports participation significantly higher in control subjects. Mean T1p relaxation times of the patellar (46.8 vs 46.1 milliseconds (ms), 𝑝 = 0.94) and trochlear cartilage (50.9 vs 50.1 ms, 𝑝 = 0.52) did not significantly differ between patients and control subjects. In addition, no significant difference was seen between patients and control subjects in mean T2 relaxation times of patellar (33.4 vs 32.8 ms, 𝑝 = 0.16) and trochlear cartilage (36.8 vs 36.6 ms, 𝑝 = 0.70) (see Table 1).

Conclusions: Our findings suggest that cartilage composition, measured by T1p and T2 mapping, does not play a role in the etiology of PFP. However, follow-up research will demonstrate potential regional differences within the patellar and trochlear cartilage.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 and T1p relaxation times (ms) of trochlear and patellar cartilage (Mean(sd)).</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Patients (N=59)</th>
<th>Controls (N=67)</th>
<th>Mean difference (±95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2 trochlea</td>
<td>36.81 (2.55)</td>
<td>36.63 (2.39)</td>
<td>0.18 [-0.69, 1.05]</td>
<td>0.70a</td>
</tr>
<tr>
<td>T2 patella</td>
<td>33.41 (2.86)</td>
<td>32.82 (2.56)</td>
<td>0.59 [-0.36, 1.55]</td>
<td>0.16b</td>
</tr>
<tr>
<td>T1p trochlea</td>
<td>50.85 (3.57)</td>
<td>50.13 (4.03)</td>
<td>0.72 [-0.72, 2.17]</td>
<td>0.52b</td>
</tr>
<tr>
<td>T1p patella</td>
<td>46.79 (4.21)</td>
<td>46.09 (4.43)</td>
<td>0.70 [-0.94, 2.34]</td>
<td>0.94b</td>
</tr>
</tbody>
</table>

sd= standard deviation  
CI= confidence interval  
a: adjusted for BMI, sports participation and gender  
b: adjusted for BMI and sports participation