

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

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**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  $\mu$ -CT analysis, respectively.

**Results:** In the DMM knee of all experimental groups, osteoclast-created subchondral bone cysts (SBCs) were confirmed in the weight-bearing area of medial tibia. The diameter of SBCs in DMM+walk (0-8w) and DMM+walk (4-8w) groups were significantly small compared with sham knee and DMM+walk (0-4w) groups ( $P < 0.05$ ). In addition, trabecular subchondral bone volume/total volume (Sb BV/TV) underneath subchondral bone plate was decreased in DMM group compared with sham knee ( $P < 0.01$ ) which was prevented by treadmill exercise. Particularly the Sb BV/TV in DMM+walk (0-8w) and DMM+walk (4-8w) groups was high and similar extent with sham knee. These preventive effects on SBCs growth and subchondral bone porosity in DMM+walk (0-8w) and DMM+walk (4-8w) groups coincided with the prevention of cartilage degeneration as evaluated by the Osteoarthritis Research Society International (OARSI) score and Subchondral Bone (SB) damage score, and number of osteocyte death. Spearman's rank test revealed that there was significantly positive correlation between the OARSI score and SB damage score ( $P < 0.01$ ,  $r = 0.90$ ).

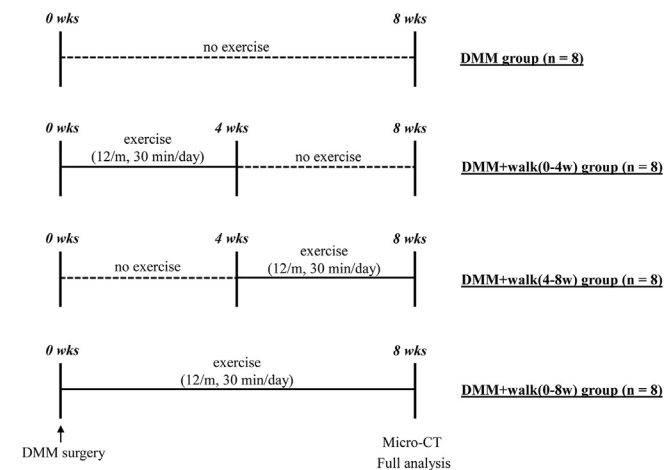


Figure 1. Experimental design including exercise duration, exercise timing, and analytic point of each experimental group.

**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

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**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 year, 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-monocyte derived osteoclasts were placed on either young bone (calf 9 months), old bone (cow 72 months), subchondral bone (calcified cartilage) or articular cartilage, and followed for up to 7 days. The effect of the matrices on osteoclast activity was assessed by TRACP activity, CTX-I and calcium, and the alterations in osteoclast subtype were assessed using western blotting for osteoclast markers.

**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 significantly 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 T1 $\rho$ AND T2 MAPPING MRI SHOW NO DIFFERENCE IN CARTILAGE COMPOSITION BETWEEN PATIENTS WITH PATELLOFEMORAL PAIN AND HEALTHY CONTROL SUBJECTS

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**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 (PFOA), 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