Letters to the Editor

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Moderate-impact exercise is associated with decreased severity of experimental osteoarthritis in rats

Sir, We read with interest the article by Manninen et al. [1] reporting that moderate physical exercise is associated with a decreased risk of knee osteoarthritis (OA). We have recently investigated the influence of moderate exercise on the course of an OA model induced by anterior cruciate ligament transection (ACLT) in the rat. ACLT, a well-known model of OA that was characterized initially in various species (e.g. dog, rabbit, monkey [2]), has recently been validated in the rat [3].

Sixty male Wistar rats (200 g) underwent ACLT under anaesthesia (ketamine 50 mg/kg + acepromazine 1.25 mg/kg intraperitoneally) according to Williams et al. [4], with minor modifications. On day 0, a parapatellar skin incision was performed on the medial side of the right knee joint and then on the medial side of the patellar tendon. The patella was then dislocated laterally to provide access to the joint space and the anterior cruciate ligament was transected in the flexed knee. A positive anterior drawer test confirmed complete transection of the ligament. The joint was then irrigated with sterile saline to avoid ancillary inflammation, and a purpose-made suture was inserted. The left knee joint was sham-operated as a negative control. Animal welfare guidelines were adhered to at all times.

Rats that had received ACLT were then assigned randomly to two groups: (i) animals in the control group were allowed to move freely in standardized cages; and (ii) animals in the exercise group were made to run on a training mill (LE 8700; LSI Letica, Barcelona, Spain) at a constant speed of 30 cm/s for 30 min, thus leading to a total distance run of 15 km over 28 days. A previous study [5] demonstrated, in naive mature rats, that a running distance of 15 km may lead to moderate knee OA compared with running for 30 km, which induces severe OA. In our experience, running 15 km induces no OA (as compared with running for 30 km, which induces severe OA). In our study, 15 km induces OA in naive mature rats, and we have recently investigated the influence of moderate exercise on the development of surgically induced OA in the rat. It has been established previously that a high load effort has a detrimental effect on the operated knee in the early postoperative period [6].

On day 7, there were marked synovitis and surface alterations consisting of fibrillation. The severity of chondral lesions peaked on day 7 and was then stable until day 28. Chondral erosions predominated on the medial tibial plateau, and were present to a lesser extent on the medial femoral condyle in weight-bearing areas. On the other hand, only moderate lesions occurred on the patella. Similar changes were noted macroscopically. Apoptotic events peaked on day 7 and were then stable until day 28, occurring in approximately 12% of chondrocytes vs 1.5% in the control naive rats. These findings are similar to those reported by Stoop et al. [3].

No body weight loss was found in the exercised group compared with the control group. Neither febrile reaction nor loss of spontaneous nocturnal mobility was found in the exercise group, and macroscopic score and histological lesions were significantly decreased (P<0.05) in this group on days 14 and 28 (Fig. 1). Chondrocytic apoptotic events were significantly less pronounced in the exercise group on days 7, 14 and 28.

To our knowledge, this is the first experimental study demonstrating the beneficial influence of moderate exercise on the development of surgically induced OA in the rat. It has been established previously that a high load effort has a detrimental effect on the operated knee in the early postoperative period [6].

![Fig. 1. Time course of OA lesions in control (open columns) and exercised rats (grey columns) that had been subjected to ACLT. Histological grading was recorded blindly by two observers (LG, SE). Values are mean and s.e.m. for five rats. *P<0.05, exercised rats vs controls at the same times (Student’s t test). (A) Histological grading according to Mankin’s score, demonstrating the significant beneficial effect of moderate exercise on days 14 and 28. (B) Time course of apoptotic events assessed by immunostaining of activated caspase 3. Note the early apoptotic events in the control group and the significant beneficial effect of exercise on days 7, 14 and 28.](https://academic.oup.com/rheumatology/article-abstract/42/5/692/1784718/228297)
meniscectomized rats and, to a lesser extent, control rats [5]. Recent experimental studies in equine articular cartilage also showed ambivalent effects of strenuous vs. moderate exercise on the metabolism and aspect of articular cartilage [9, 10]. This ambivalence is well known in the clinic [11], where it has been established that OA is associated with heavy lifting, farming and elite sports activity but that moderate exercise does not seem to increase the risk of OA [12]; under certain circumstances it may even prevent spontaneous knee OA in the hamster [13] or in humans in the clinic [1].

As the use of a training mill makes it possible to measure the effort applied to weight-bearing joints, we actually assess a ‘dose–response’ relationship for exercise in ACLT rats, and also the contributions of endogenous proinflammatory cytokines and anti-apoptotic mediators such as Hsp70, which is overexpressed during repeated loading [14].

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