Gait Analysis of a New Murine Model of OA Induced by Achilles Transection and Treadmill Running

Introduction

We recently reported the development of a non-surgical murine model of OA in which unilateral joint degeneration is initiated by two intra-articular injections of TGFβ1 (to mimic injury), followed by enforced uphill treadmill running. In this model, only minor joint changes were seen after TGFβ1 injections alone, or treadmill running alone. However, TGFβ1 and treadmill combined, resulted in widespread pitting, roughening and erosion of cartilage surfaces along with fibrous in-growths from adjacent peri-articular margins. The model illustrates how overload can accelerate OA progression in an invasively "injured" knee joint. To investigate the effect of altered load without invasive knee joint injury, we have developed an alternative model of knee joint injury, induced by unilateral transection of the Achilles tendon followed by treadmill running. We report here a quantitative characterization of specific gait changes induced in each hind limb by this procedure as well as accompanying knee cartilage pathology.

Methods:

Mice (12 wk male C57BL6) were bred in-house and protocols approved by our IACUC. The Achilles tendon was transected (or not) in the left hind limb only and mice were rested for 3 days before running on a treadmill (TM) at 32 cm/sec for 25 min daily on a 17 degree uphill gradient or maintained at cage activity. Gait parameters were analyzed. Treadscan (Treadscan, Cleversys Inc.) in both hind limbs were obtained pretreatment, and after 7, 14, 21, and 28 days of treadmill running (or cage rest) and performed in the morning before treadmill running for that day. Macroscopic changes were visualized in both left and right knees as described. Statistics: For each gait parameter (stance, brake, propulsion) in each hind limb, the value on that day was normalized to the pretreatment value. The mean +/- SD (n=3) of the normalized values were calculated and Students t-tests were performed to evaluate differences between the normalized gait metrics and unity. P-values less than 0.05 were considered statistically significant.

Results:

Knee joint pathology. Macroscopic inspection at 28 days showed that no obvious erosive changes were observed in each knee for mice kept under cage activity with or without transection (top panels). However, with treadmill challenge, cartilage surface erosion and peri-articular fibrosis were evident in the right (i.e. contralateral) knee and were largely confined to the postero-lateral tibial plateau (boxed areas, Fig.1) and the patellar groove, together with adjacent areas of both medial and lateral femoral condyles (not shown). Only minor changes developed at this site in the left (transected) leg or either leg without transection (Fig.1 bottom panels). Gait analysis of mice in OA model. We found significant gait alterations relative to pretreatment (see Table 1, significant data bold and underlined) during the TM phase. In the operated (L) leg there were increased stance times (of 46% (shown as 1.46) and 39% (shown as 1.39) and propulsion times (83% and 59%) on days 21 and 28 respectively. Most strikingly, there was a marked and sustained increase in the brake time in the contralateral (R) limb such that increases of 64%, 41% (p=0.09), 45% and 39% were seen on days 7, 14, 21, and 28 respectively. Gait analysis of mice with transection showed a trend (p=0.13) toward an increase in propulsion time in the left leg on day 14 (Table 1), which was observed (51% at p<0.05) in mice without TM. In contrast, multiple increases in brake time seen in the right limb of TM treated mice were absent from cage only mice (Table 1). The possibility that gait parameters might be influenced by the "familiarity" of only the TM mice to the measurements was essentially eliminated by the finding that in the absence of tendon transection, TM and caged mice showed no differences in gait measures (data not shown).

Discussion:

We have developed a murine model of OA in which knee joint pathology in the right knee is induced by Achilles tendon transection in the left limb. This is an important step forward in murine OA modeling since, unlike the destabilization of the medial meniscus (DMM) model and TGFβ/TM model, OA-like changes in the right (contralateral) knee cannot be due to, or accelerated by, factors accompanying local and invasive tissue injury. Instead, right knee pathology in the current model appears to result from a combination of aberrant joint loading and joint overuse. Aberrant joint loading is implicated for two reasons. Firstly, the cartilage erosion and fibrosis is confined to the posterior aspect of the lateral tibial plateaus, suggesting a

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