THE INFLUENCE OF CYCLIC CONCENTRIC AND ECCENTRIC SUBMAXIMAL MUSCLE LOADING ON CELL VIABILITY IN THE RABBIT KNEE JOINT

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SUMMARY
Cartilage loading is associated with the onset and progression of osteoarthritis and cell death may play an important role in these processes. Although much is known about cell death in joint impact loading, there is no information on joints loaded by muscular contractions. The aim of this study was to determine chondrocyte viability for sub-maximal muscle loading of joints. We hypothesized that sub-maximal muscle loading of the knee does not cause chondrocyte death.
16 rabbits received 50 mins of unilateral, cyclic eccentric (n=8) or concentric (n=8) knee loading. Muscle activation for these dynamic conditions was equivalent to activation producing 20% of maximum isometric force. Contralateral joints served as unloaded controls. Cell viability was assessed using confocal microscopy.
Eccentric contractions produced greater knee loading than concentric contractions. Sub-maximal contractions caused a significant increase in cell death in the loaded knees compared to the unloaded controls, and eccentric loading caused significantly more cell death than concentric loading.
In conclusion, cyclic sub-maximal muscle loading of the knee caused increased chondrocyte death. These findings suggest that low levels of joint loading for prolonged periods, as occurs in endurance exercise or physical labour, may cause chondrocyte death, thereby predisposing joints to degeneration.

INTRODUCTION
There is evidence that cell death plays an important role in cartilage aging and OA development[1,2]. Cartilage loading in sports and heavy labour activity is likely associated with the onset and progression of osteoarthritis [3,4]. In vitro experiments have demonstrated that cyclic loading with peak contact stresses of 3.5-6.9 MPa produced rapid cartilage damage[5,6]. These contact stresses are well within experimentally observed and theoretically calculated joint contact pressures for locomotion, and although there might be species-, age-, and joint- specific differences, and although in vitro approaches might not well represent the loading environment in the intact joint, there is a possibility that relatively benign dynamic loading of joints over an extended period, such as in endurance sports, may kill articular cartilage chondrocytes[5].
The aim of this study was to evaluate the influence of muscle generated eccentric and concentric submaximal joint loading on chondrocyte viability. We hypothesized that relatively low levels of muscular loading of the knee, even over a prolonged period, would not cause an increase in chondrocyte death.

RESULTS AND DISCUSSION
Eccentric and concentric contractions at an activation equivalent to 20% of maximum isometric force at 50Hz and 100 degrees of knee flexion resulted in significantly different average forces for the concentric and eccentric contractions (p=0.012). Across the entire knee, the percentage of cell death was significantly greater for the eccentric compared to the concentric exercise group (p<0.001) and for the eccentric and concentric compared to the control group (p<0.001 for both comparisons) (Figure 1 and 2). Looking at regional distribution, the cartilage surfaces of the loaded joints showed significantly increased rates of chondrocyte death for the inferior patella, central and lateral/medial regions of the femoral groove as well as for certain regions of the condyle.
Figure 1. Example from the medial femoral groove cartilage (presented as 3D animation of a vertical stack). Green dots represent live cells, red dots indicate dead cells. A) eccentric muscle stimulation; B) concentric muscle stimulation; C) control.

Figure 2. Average chondrocyte death rate for the whole joint.

and the tibial plateau. Cyclic submaximal joint loading by eccentric, and to a lesser extent concentric, muscle stimulation leads to an increased rate of chondrocyte death in the superficial layers of patellofemoral and tibiofemoral cartilage. The joint loading applied in this protocol was well within the physiologically observed range. However its duration over a 50 min loading period was much longer than the average rabbit would hop for. Thus, our model is representative of “excessive” exercise as one might encounter in a marathon run or intense physical labour. These findings support the idea that forces within physiological amplitudes can lead to increased chondrocyte death if applied over an extended period. Since chondrocyte death has been associated with early joint degeneration [1:2:7], exercise or work of excessive duration might play a role in the onset and progression of primary OA. Eccentric joint loading leads to increased chondrocyte death, which might be consistent with findings in workers with heavy labour jobs that include great amounts of eccentric contractions, such as in bending, squatting and descending stairs[8;9]. Regional distribution of chondrocyte death patterns could be due to regional differences of the applied force or susceptibility of the cartilage to these loads. Although there are no data on the regional distribution of joint loads in the rabbit knee subjected to eccentric and concentric loading, it can be assumed that the regions of high chondrocyte death may correspond with high load-bearing areas of the knee, but this assumption needs independent verification by quantifying cell deaths and mechanical loading of the articular surfaces simultaneously.

It has been shown in vitro that chondrocytes from different regions of a joint respond differently to mechanical loads[10]. Therefore, another explanation for our regional distribution of chondrocyte death occurrence might be the ability of chondrocytes to withstand mechanical loading, either because chondrocytes in some areas might be protected better by the cartilage matrix and the epi- and peri-cellular matrix, or because chondrocytes in some areas are built tougher than in other areas.

CONCLUSIONS
Extrapolating our findings to chronic training, it may be speculated that excessive, cyclic, submaximal loading of healthy cartilage leads to an increasing number of dead chondrocytes which would increasingly compromise the cartilage’s ability to maintain its extracellular matrix structure and biomechanical properties. An accumulation of such damage may lead to OA. Since eccentric loading created the highest percentages of chondrocyte death, the results of this study may have important implications for sport activities, training regimes, ergonomic factors, and rehabilitation protocols that contain a high percentage of eccentric exercise. However, to confirm the link between excessive joint loading at a physiological range of load and OA long term studies relating these factors are required.

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REFERENCES