

of radiolabeled anti-rat type II collagen antibody were detected in the synovial fluid 10 minutes and 24 hours post-IA administration relative to the non-specific antibody.

Conclusions: Rapid clearance of a non-specific antibody from the synovial fluid and joint tissues is observed after IA dosing to a normal rat knee joint. The data highlights that if sustained drug exposure is required for efficacy, the retention time of the therapeutic needs to be increased. Sustained retention of an anti-collagen II antibody in the rat joint suggests that binding to a resident protein may extend antibody retention time.

101

IN VITRO VALIDATION OF A VARUS LOADING DEVICE IN THE RABBIT KNEE

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Purpose: Methods of producing relevant and quantifiable load alterations *in vivo* with which to study load-induced cartilage degeneration are limited. A novel loading device has been developed to apply a varus moment to the knee creating a chronic overload to the medial compartment of the knee while allowing normal joint function. The objective of this study is to confirm the change in load in the medial compartment of the rabbit knee with application of a known target load.

Methods: The increase in medial compartment compressive load generated by the Varus Loading Device (VLD) was measured directly *in vitro* and compared to the predicted values. The VLD is mounted via transcutaneous bone plates attached to the lateral aspect of the femur and tibia (Fig. 1). The VLD allows moments to be applied only during the designated treatment period, at other times the moment can be disengaged by detaching the distal portion of the load link.

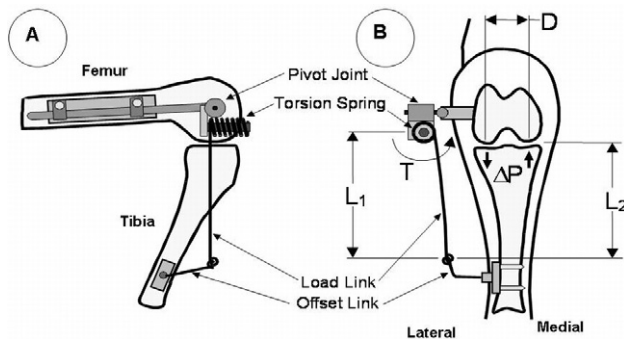


Figure 1. VLD applied to a hind limb: (A) lateral view, (B) anterior view. Application of the VLD results in an increase in compressive load in the medial compartment by an amount ΔP . The change in load can be modulated in a controlled manner by setting the spring torque as shown by Eqn. 1 where: ΔP = change in contact load, T = torque setting of the spring, D = intercompartmental moment arm, L_1 = load link moment arm, and L_2 = tibia moment arm. Eqn 1: $\Delta P = T/D \times L_2/L_1$.

The VLD was installed on five, NZW rabbit, hind limbs. The medial joint capsule was opened and the medial tibial plateau was resected to a level 6 mm below the joint line. A load cell, 6mm dia. x 6mm tall, (ALD Design, NY) was inserted in the resection cavity and cemented in place, maintaining the original level of the joint line. The medial femoral condyle contacted the load sensor ensuring that the entire compressive load developed in the medial compartment was measured by the load cell. The femoral head was mounted in a ball joint and the distal tibia was fixed in a clamp, positioned such that the femur was horizontal, and the flexion angle was approximately 115° to orient the tibial

plateau horizontally. A 100 N weight was attached to the femur just proximal to the knee joint. This generated a compressive tibio-femoral load approximately equally divided between the medial and lateral compartments to simulate the physiologic joint load normally present in the knee due to muscle activity, gravity and inertial loads. The compression load cell was zeroed with this static load in place. Moment arms were measured. The target torque level was set and measured using a spring scale acting over the moment arm L_1 . Three values of ΔP were targeted: 25 N, 50 N, and 100 N. Using Eqn. 1, the spring torque required to generate each of these was calculated and applied to the VLD in succession and the actual ΔP generated, as measured by the load cell, was recorded.

Results: For all data points, the measured ΔP was within 14% of the target ΔP (Fig. 2). The slope of the least squares fit line through the data points was not significantly different than 1.

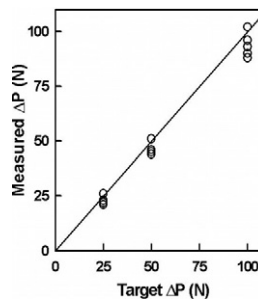


Figure 2. Measured vs. target values of ΔP with VLD application.

Conclusions: These results demonstrate the overall feasibility of applying a known compressive overload, ΔP , to the medial compartment of the knee using the VLD. The ability to apply consistent load alteration to the knee will allow the future study of the dose response of articular cartilage to quantified levels of load alteration *in vivo*.

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102

DIFFERENCE IN OSTEOPHYTE FORMATION AND SMAD SIGNALING BETWEEN MURINE INFLAMMATORY ARTHRITIS AND OSTEOARTHRITIS

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Purpose: Osteophytes are a hallmark of osteoarthritis. In rheumatoid arthritis no osteophytes are found but profound bone deposition is observed in ankylosing spondylitis. In animal models the development of osteophytes is observed in both inflammatory and degenerative joint diseases. In murine (osteo)arthritis models, osteophyte formation appears to be the results of two processes. New bone deposition via differentiating stem cells and endochondral ossification or through intramembranous deposition by osteoblasts. We studied whether osteophyte formation differs between murine inflammatory arthritis (IA) and osteoarthritis (OA), and if dissimilar, what factors play a role in this unequal osteophyte development.

Methods: We compared osteophyte formation in the following OA models; spontaneous OA in Str/ort and collagenase-induced osteoarthritis in C57Bl/6 mice. Inflammatory arthritis was studied in collagen-induced arthritis in DBA-1J mice, streptococcal cell wall-induced arthritis in C57Bl/6 mice and serum transfer-induced arthritis in C57Bl/6 x 129Sv mice. Knee joints were dissected at early as well as advanced time points during the development