Serum Biomarkers In A Novel In Vivo Model Of Post-traumatic Osteoarthritis

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Introduction: Osteoarthritis (OA) affects ~90% of people older than 65, and associated costs top $100 billion annually in the USA alone. Post-traumatic osteoarthritis (PTOA) is caused secondarily due to an injury of the joint, and accounts for approximately 12% of the overall OA burden (Catterall et al., 2010). The risk of developing PTOA after a joint injury is as high as 50%. However, it is not well understood why certain patients develop PTOA after joint injury and other patients do not despite having similar joint injuries. Further, there are currently now diagnostic modalities available to determine if a patient will develop PTOA after a joint injury. Because the clinical timeframe of PTOA development is often years, it is difficult to perform longitudinal studies within the human patient population to identify factors that can be used as diagnostic markers for determining the risk of PTOA development. Therefore, accurate translational animal models of PTOA are needed to improve our understanding of PTOA development and identify accurate diagnostic modalities to assess the risk of PTOA development after joint injury clinically (Little et al., 2013). The purpose of the present study was to assess the serum concentration of various cartilage degradation and synthesis biomarkers using a novel canine PTOA model. In this model articular cartilage and subchondral bone pathology is created on the medial femoral condyle using a single impact delivered arthroscopically. It is theorized that biomarkers indicative of cartilage degradation would increase and biomarkers indicative of cartilage synthesis would decrease 12 weeks after impact.

Methods: With ACUC approval, adult purpose-bred research dogs (mean weight 26.5 kg) were premedicated and anesthetized. Under aseptic surgical conditions, impact injuries were delivered to the medial femoral condyle of the right knee of each dog (n=16 knees) arthroscopically using a custom-designed, spring-driven impactor with an 8 mm diameter tip. The right knee was impacted at 40 N and the left was sham impacted. Dogs recovered uneventfully from surgery and received analgesics for 48 hours and then as needed based on physical parameters indicating the presence of pain. The dogs were restricted to their kennels with monitored daily out-of-kennel exercise in a confined area. Whole blood was collected and spun down for serum at Day 0 (pre surgery) and at 12 weeks. ELISA biomarker assays were run on serum for Cartilage Oligomeric Matrix Protein (COMP), C-telopeptide of type I collagen (CTX-I), C-telopeptide of type II collagen (CTX-II), N-propeptide of collagen IIA (PIIANP), Aggrecan chondroitin sulfate 846 epitope (CS846) and Collagenase-generated cleavage epitope of type II collagen (C2C).

Results: Serum biomarker (Figure 1): At 12 weeks the concentration of CS846 was significantly (p<0.001) lower than at time 0. The serum concentration of PIIANP, CTX-I, CTX-II C2C, and COMP did not change significantly from time 0 to the 12 week time point.
Discussion: The impact model described here results in an acute procedure resulting in immediate damage to the cartilage and bone of the condyle. Similar to the human clinical patient population, the concentration of the biomarkers assessed in this model were highly variable from animal to animal, did not change much from time 0 to 12 weeks after injury. A significant decrease in the proteoglycan synthesis marker CS846 was observed, indicative of a potential decrease in proteoglycan synthesis 12 weeks after impact. While detectable levels of all collagen degradation (C2C, COMP, CTX-I and CTX-II) and synthesis (PIIANP) were seen in the serum of these animals, they do not indicate a significant change in the collagen turnover and metabolism of the cartilage tissue and bone that can be detected in the serum at this time point. Acute trauma has been categorized into 3 phases over an approximately 2 week timeline. Phase 1(early) characterized by cell death and inflammation, Phase 2 (intermediate) characterized by a balancing of catabolic and anabolic metabolism, and Phase 3 (late) where there is limited remodeling (Anderson et al, 2011). Therefore it is possible that by 12 weeks, the major initial remodeling response to the injury has already occurred and was missed by waiting until the 12 week time point to assess these biomarkers in the serum. These data would indicate that assessing the serum biomarker levels of a patient 12 weeks after joint injury may not be the appropriate time to identify the initial response of the cartilage and bone to the joint injury. Therefore, we theorize that early assessment after injury to identify changes in the serum biomarker concentrations indicative of cartilage and bone turnover may be more diagnostic of the level of damage to the tissue, and indicative of potential for PTOA development. Ongoing studies will monitor the dynamics of the changes in the biomarkers at earlier time points as well as over a longer period of time to determine the dynamics of these biomarkers in the serum as the lesion increases in size and progresses to the later stages of OA.

Significance: The data from this study indicates that assessing patients 12 weeks after injury for the biomarkers would not be diagnostic for the development of PTOA clinically. Future studies will assess patients and the model at earlier time points to assess the potential for immediate changes in cartilage matrix turnover biomarkers to predict the development of PTOA after injury.
Figure 1: Mean (±SD) serum biomarker concentrations at Day 0 and Week 12. * = significant decrease from day 0 to week 12.
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