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Development of a Large Animal Model of Osteochondritis Dissecans (OCD) of the Knee

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Introduction

OCD is a disorder of bone and cartilage in young persons that can engender disabling pain and precipitate the early onset of osteoarthritis (OA).[1] While OCD lesions can manifest in any joint,[2] 77-85% of lesions occur in the lateral aspect of the medial femoral condyle.[3,4] OCD lesions are typified by a disruption of the continuity of the subchondral trabecular architecture, with this discontinuity sometimes extending to the articular cartilage surface. OCD can progress across a continuum, from stable 'progeny' lesions with intact cartilage to completely dislocated progeny fragments of cartilage and associated underlying bone.[5] The etiology of OCD is not well understood, with studies suggesting causative factors such as repetitive microtrauma, vascular insufficiency, primary osteonecrosis, and genetic/developmental abnormalities, though the pathophysiology is most likely multifactorial.[6] Current practice for OCD treatment is lesion specific, depending on many factors including stability, location, and bone/cartilage quality, but lacks evidence-based criteria. While spontaneous OCD-like lesions have been investigated and experimental models in small animals have been attempted,[7] there is currently no large animal model of OCD in which to evaluate novel surgical treatments. In this study, we developed a large animal model of OCD in the stifle joint of the Yucatan minipig. We hypothesized that by surgically creating an osteochondral defect and repairing it with a biodegradable membrane interposed between the 'progeny' fragment and the 'parent' bone/cartilage, an OCD-like lesion would develop. To test this hypothesis, we evaluated short-term bone and cartilage changes when two different degradable materials (with or without fenestrations) were placed in the defect.

Methods

Bilateral osteochondral lesions (9.5 mm x 12.5 mm) were created in the medial femoral condyles of nine 6-month old Yucatan minipigs. Before replacing the 'progeny' fragment, a biodegradable membrane was sandwiched between the progeny and parent bone (Figure 1). Five different treatment groups were evaluated at 2 weeks: a slowly degrading nanofibrous poly(ε-caprolactone)(PCL) membrane (n=4), a fenestrated PCL membrane (fenPCL, with 1.5 mm holes covering 25% of surface area, n=4), a commercially available collagen membrane (Biogide®, BG, n=3), and a fenestrated BG membrane (fenBG, n=3). Additional defects were created as controls (Ctrl, n=4), where the progeny was reinserted into the defect without an interposed layer. Six 6-0 sutures were placed at the defect boundary to provide initial stability. Animals were sacrificed at postoperative day 14 and the lesion was evaluated by gross inspection, fluoroscopy, micro-CT, and histology. To quantify changes between groups, a scoring system based on gross appearance (0-2), fluoroscopy (0-2), and micro-CT (0-6) was established, where lower numbers indicated 'normal' and scores of 4-7 indicated an 'OCD-like' appearance. We additionally quantified bone volume per total volume (BV/TV) in a defined region surrounding and inclusive of the defect using micro-CT. Statistical analysis was carried using one-way ANOVA with Bonferroni post-hoc test for micro-CT and a Kruskal-Wallis test with Dunn's multiple comparison post-hoc for the OCD Score.

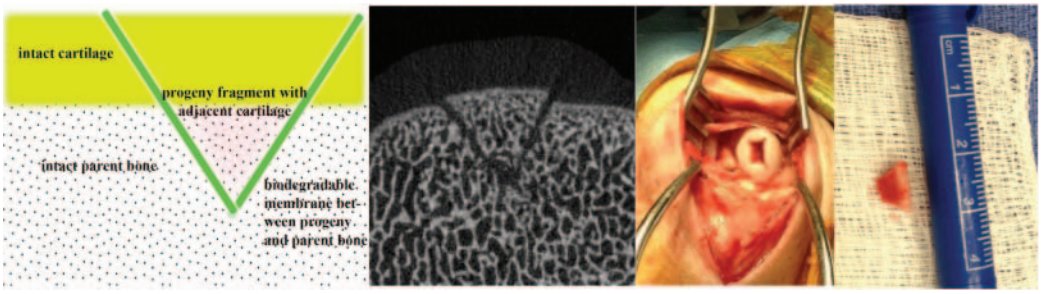

Figure 1. Left to right: schematic of OCD lesion, micro-CT in coronal plane of lesion on day 0, intraoperative surgical site after creation of the lesion (before insertion of progeny fragment), and higher magnification view of progeny fragment (with scale bar).

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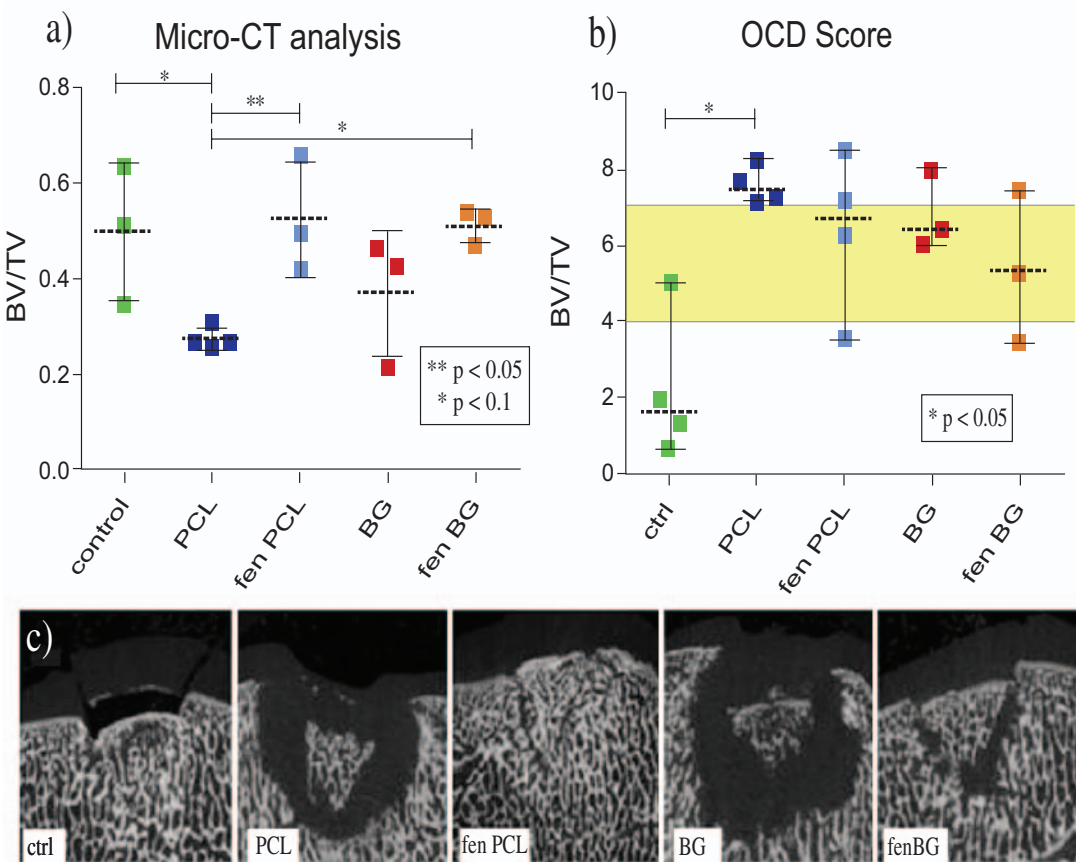

Figure 2. a) Micro-CT analysis of bone volume per total volume in a defined region including the lesion. b) Total 'OCD score' for each condition. An ideal range (between completely stable/connected (7 points) is indicated by the shaded region. c) Ex vivo micro-CT images from the center of the lesion on postoperative day 14 for each group (coronal view).

Results

Surgical creation of an osteochondral defect on the femoral condyle proceeded without complication, and animals recovered to normal ambulation within 2 days of surgery. On day 0, there was clear separation between parent and progeny fragment when the interpositional membrane was placed (Figure 1). After 14 days, control groups showed marked healing of the subchondral bone, though some lesions were slightly depressed relative to the articular surface (Figure 2c). Condyles treated with PCL or BG membranes showed substantial remodeling at this time point, with clear loss of bone in both the progeny fragment and surrounding parent bone. Conversely, both fenestrated groups (fenPCL and fenBG) showed less bone loss and in some instances, small trabecular bridges forming between the parent and progeny (Figure 2c). From histological sections, there was no evidence of integration in the cartilage layer in any group, and some fibrous tissue was observed between the parent and progeny

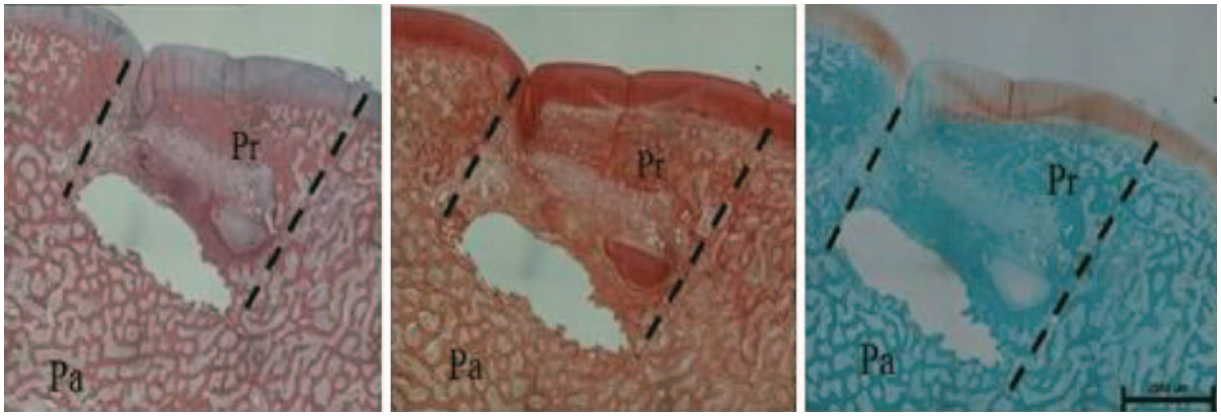

Figure 3. Histological sample of an OCD-like lesion created after placement of a PCL membrane between the Parent (Pa) and Progeny (Pr) fragment (sagittal view). Evidence of remodeling in both progeny and parent bone is apparent, as is fibrous tissue in the defect. Osteotomy sides are marked by dotted lines. Scale bar: 2mm. Stains left to right: Hematoxylin & Eosin, Picrosirius Red, Safranin O & Fast Green.

fragments (Figure 3). Micro-CT quantification showed significant differences in BV/TV between the PCL and fenPCL groups, control and PCL groups, and PCL and fenBG groups, but no differences between any other group pairs (Figure 2a). Grading by six blinded reviewers (using the 'OCD-like' scoring system) showed a significant difference between Control and PCL groups ($p<0.05$) and indicated that several groups (fenPCL and fenBG) fell within the target window (Figure 2b).

Discussion

In this pilot study, we successfully produced an osteochondral lesion with hallmarks of OCD in a large animal model by situating a semi-permeable membrane between the parent bone and progeny fragment. Control groups showed evidence of bony apposition in the subchondral trabecular space, while inclusion of either biodegradable membrane instigated significant bony remodeling of the progeny fragment and the parent bone. Fenestrations within the membrane decreased the extent of this remodeling. Quantitative data and semi-quantitative grading of samples provided outcome parameters that were able to distinguish treatment groups from controls. While these results suggest that an 'OCD-like' state is present at this early time point, additional animals are now being investigated over longer periods of time to determine whether this is a transient phenomenon or whether placement of these interpositional membranes promotes fibrous non-union over a longer duration. Overall, our results suggest that it will be possible to generate an OCD-like model in the minipig, opening the door for the future development of novel surgical strategies.

Significance

This large animal model may serve as reliable basis for the development of novel surgical approaches for the treatment of OCD lesions.

Acknowledgments

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