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THU0060

KNEE JOINT DISTRACTION INDUCED SHIFT FROM CATABOLIC TO ANABOLIC STATE OCCURS AFTER DISTRACTION PERIOD

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Background: Knee joint distraction (KJD) is a validated joint-preserving treatment strategy for severe osteoarthritis (OA) that provides long-term clinical and structural improvement. Human trials and animal models indicate clear cartilage regeneration from 6 months and onwards post-KJD [1]. Recent work showed that during distraction, the balance between catabolic and anabolic indicators is directed towards catabolism, as indicated by collagen type 2 markers, proteoglycan (PG) turnover and a catabolic transcription profile.

Objectives: To investigate the cartilage changes directly and 10 weeks after joint distraction in order to elucidate the shift from a catabolic to an anabolic cartilage state.

Methods: Knee OA was induced bilaterally in 8 dogs according to the groove model. After 10 weeks of OA induction, all 8 animals were treated with knee joint distraction, employing the left knee as an OA control. After 8 weeks of distraction, 4 dogs were euthanized (KJD_{direct}) and after 10 weeks of follow-up the 4 remaining dogs (KJD₊₁₀). Macroscopic and microscopic cartilage degeneration was assessed using the OARSI canine scoring system. RT-qPCR was used to determine relative expression of aggrecan (ACAN), collagen type II (COL2a1), cartilage oligomeric matrix protein (COMP) and matrix metalloproteinase-3 (MMP3) in the cartilage. PG content was determined by the Alcian Blue assay and the synthesis of PGs was determined using ³⁵SO₄²⁻ as a tracer, as published before.

Results: Macroscopic cartilage damage of the tibial plateau in the KJD_{direct} group was higher as compared to the OA control (OARSI score: 1.7±0.2 vs 0.6±0.3; *p* < 0.001). For KJD₊₁₀ this difference persisted (OARSI score: 1.4±0.6 vs 0.6±0.3; *p* = 0.05). Microscopically, an increase in the total OARSI score was seen after 10 weeks post-KJD. This was mainly due to an increase of chondrocyte clusters at 10 weeks of follow-up, resulting in an increased sub score chondrocyte pathology. Remarkably the sub score intensity of proteoglycan staining decreased directly after KJD (indicating a loss of PGs) but increased after 10 weeks of follow-up suggesting a mixed response depending on the item scored.

Cartilage gene expression analysis showed downregulation of COL2a1 (-1.3 ± 0.3), ACAN (-4.4 ± 1.0, *p* < 0.01) and COMP (-1.7 ± 0.5) in the _{direct} group compared to OA control suggesting enhanced catabolic activity during KJD. In contrast, after 10 weeks of follow-up the expression of COL2a1 and COMP were increased as compared to the OA control (2.6 ± 1.1 and 2.5 ± 1.2 respectively) as well as compared to the KJD_{direct} situation (3.3 ± 1.4 and 4.2 ± 2.0). Expression of MMP3 was upregulated directly after KJD (4.4 ± 0.8) and downregulated after 10 weeks of follow up (-3.3 ± 0.8).

Biochemical analysis of the tibia cartilage of the KJD_{direct} group revealed a lower PG content compared to the OA joint (20.1±10.3mg/g vs 23.7±11.7mg/g). At 10 weeks post-KJD this difference in PG content was gone (24.8±6.8mg/g vs 25.4±7.8mg/g). The PG synthesis rate directly after KJD appeared significantly lower vs. OA (1.4±0.6 nmol/h.g vs 5.9±4.4 nmol/h.g; *p* < 0.001). 10 weeks post-KJD this difference was not detected (3.7±1.2 nmol/h.g vs 2.9±0.8 nmol/h.g), and the synthesis rate in the distracted knee was increased compared to directly after distraction (*p* < 0.01) indicating a shift upon follow-up.

Conclusion: Further in-depth investigation of the material is ongoing and also includes the other joint tissues such as the bone and the synovial tissue. Irrespective, these first results on cartilage changes suggest that the shift from a catabolic to an anabolic state occurs within the weeks after joint distraction. As such, the post-distraction period seems to be essential in identifying key-players that support intrinsic cartilage repair.

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THU0061

EVALUATION OF SAFETY AND EVOLUTION OF OSTEOARTHRITIC JOINTS AFTER THE ADMINISTRATION OF HETEROLOGOUS MESENCHYMAL STROMAL CELLS IN AN ANIMAL MODEL

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Background: One of the main osteoarthritis (OA) consequences is the cartilage loss. Nowadays there is not cure for the OA, so there is an intense research focused on finding a therapy to solve this problem. In this paradigm heterologous mesenchymal stromal cells (MSCH) rise as a solution. Different studies used them as a cellular therapy in order to regenerate damaged cartilage. Furthermore, MSCH have shown anti-inflammatory effects.

Objectives:

- 1) Study the safety of a single intraarticular injection of MSCH derived from healthy canine fat tissue (adMSCH) in OA joints of dogs
- 2) Observe the evolution of functionality and range of articular mobility of these treated joints 6 months after the injection.

Methods: adMSCH obtained (n=10) were phenotypically characterized by flow cytometry, including the Major Histocompatibility Complex type II (MHC-II). Those with the best morphology and growth (n=5) were used for the injection.

The infiltrated dogs (n=7) met our inclusion/exclusion criteria. The adMSCH were injected in 11 joints by 1 million of cells/kilogram of weight.

Before the infiltration we evaluated the joints (basal visit, BV), the vital signs and the animal pain by the owner (Visual Analogical Scale, VAS). The same data were collected one week after the infiltration (V1) and also studied the injected zone. Six months after treatment (V2), joint functionality and range of articular mobility were evaluated, also data of behavioural changes and pain observed by the owners.

Table 1. Functionality and range of articular mobility comparison between BV and V2. Visits column show the number of joints in that state

	Variable	Answers	Visits		t-student (p-value)	n
			BV	V2		
FUNCTIONALITY	Load changes	Normal	3	7	0.095	11
		Change load	8	4		
		Support fingers	0	0		
		No support	0	0		
	Load changes when getting up	Correctly	1	6	0.024*	11
		Position modification	10	5		
		Difficulty to get up	0	0		
		No get up	0	0		
	Lameness in cold	No lameness	1	2	0.062	11
		Mild lameness	6	9		
		Intense lameness	4	0		
		No support	0	0		
RANGE OF ARTICULAR MOBILITY	Lameness when warmed	No lameness	1	3	0.106	11
		Mild lameness	8	8		
		Intense lameness	2	0		
		No support	0	0		
	Articular passive manual mobility	Without pain	0	0	0.400	11
		Mild pain	3	5		
		Raised pain	8	6		
		Disabling pain	0	0		
	Flexion limitation	Total flexion	9	8	0.750	11
		Mild limitation	1	2		
		Severe limitation	1	1		
		No limitation	0	0		
	Extension limitation	Total extension	0	3	0.749	11
		Mild limitation	9	4		
		Severe limitation	2	4		
		No limitation	0	0		

*. Statistical significance established at *P* ≤ 0.05

Results: All cells obtained were negative for the MHC-II (0.45 ± 0.32). Vital signs did not change between BV and V1. No dog suffered by severe inflammation of the injected joint. One of them during two days had difficulty to support the load in the posterior limbs, but at the third day it performed that without difficulty. Other dog suffered mild inflammation which was solved in two days. The other animals did not show any adverse effect after the infiltration. In the V1 none of them showed any inflammation in the joint. The pain evaluation by the owners showed that all dogs have less pain or it did not increase since BV. This indicate that after the infiltration the animals did not suffer a pain increase.

Data collected in V2 showed that the joint functionality tend to improve, one of the items showing significant differences between BV and V2. The range of articular mobility did not have neither differences nor tendencies to the improvement (Table 1).

Conclusion: The administration of adMSCH did not show adverse effects, rejection, infection or complications, only a probably of a mild inflammation in the treated zone. Also, joint functionality tends to improve, so these cells seem to have, at least, an anti-inflammatory effect into the OA joint.

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THU0062

FUNCTIONAL MR IMAGING OF HUMAN MENISCUS IS ASSOCIATED WITH HISTOLOGICAL DEGENERATION

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Background: In OA, there is a close association of meniscus and cartilage pathologies. Meniscus degeneration and lesioning are critical risk factors for development of early OA. Hence, this *ex-vivo* study assessed the responses to standardized loading of human meniscus samples as a function of degeneration and based on changes in their T1, T2 and T1 ρ maps (as surrogate parameters of the tissue's functionality).

Objectives: Can meniscus functionality be visualized by serial quantitative MRI mapping techniques?

Methods: During total knee replacements, 45 meniscus samples of variable degeneration were harvested from the center of the lateral meniscus body

Figure 1. Preparation of meniscus samples and details of the MRI-compatible loading device. The lateral meniscus (a₁) was cut to standard size by use of a dedicated cutting block (a₂) to eventually obtain lateral meniscus samples (from the body region) of standard dimensions (a₃). These samples were then placed in a dedicated MRI-compatible loading device for pressure-controlled, quasi-static and torque-induced loading under simultaneous MR imaging (a₄). Two parallel support beams allowed standardized positioning in the MRI scanner's bore (a₅).

(Fig. 1a₁-a₅). After preparation to standard, samples were subject to force-controlled loading using an MRI-compatible lever device that created compressive loading by torque ((Fig. 1a₄-a₅). For each sample and loading position, MRI measurements (as detailed below) were performed in the unloaded (δ_0) and loaded configurations, i.e. loaded to 2 bar (δ_1 , 37.1 N compressive force, 0.67 Nm torque) and to 4 bar (δ_2 , 69.1 N, 1.24 Nm). Throughout all loading positions, morphological and quantitative imaging was performed using Proton Density-weighted and T1, T1 ρ , and T2 mapping sequences (3.0 T, Achieva, Philips) based on standard turbo-spin-echo, inversion-recovery, spin-lock multi-gradient-echo, and multi-spin-echo sequences. For reference purposes, histological (i.e. Pauli classification) and biomechanical measures (i.e. Elastic Modulus) were obtained for each sample. Based on Pauli sum scores, samples were trichotomized as grossly intact (n=14), mildly degenerated (n=16), and moderate-to-severely degenerated (n=15).

Results: Morphologically, loading induced deformation and flattening in all samples (Fig. 2a). For T1, homogeneous loading-induced decreases in all samples were found, irrespective of degeneration (Fig. 2b). For T1 ρ , increases in the apical zones of intact samples were observed, and decreases in degenerated samples (Fig. 2c). For T2, changes were ambiguous and incoherent (Fig. 2d).

Figure 2. Serial morphological images and functional maps of histologically moderately degenerative human meniscus as a function of force-controlled loading. Serial PDw (a), T1 (b), T1 ρ (c), and T2 maps (d) are displayed at increasing loading intensity (δ_0 : unloaded [a₁-d₁]; δ_1 : loaded to 2 bar [a₂-d₂]; δ_2 : loaded to 4 bar [a₃-d₃]). Histologically, this sample demonstrated signs of severe surface desintegration and disruption. Pauli sum score 12, i.e. moderate to severe degeneration (Pauli Grade III). In b – d, color-coded parameter value maps are overlaid onto the corresponding morphological images. Histological sections are stained with Hematoxylin-Eosin (e₁) and Safranin O (e₂).

Conclusion: Meniscus functionality may be visualized using serial quantitative MRI mapping techniques. T1 ρ may provide an imaging biomarker of relevant intra-tissue adaptations that seem to be associated with histological degeneration. The perspective evaluation of meniscus functionality may be indicative of incipient or manifest load transmission failure to the adjacent cartilage layer.

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