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Large animal models for osteochondral regeneration

Due to the lacking of a blood supply and the low cellular density of articular cartilage, this hard tissue has a limited healing capacity. Therefore, focal traumatic events causing cartilage defects rarely resolve spontaneously or are usually repaired by tissue with inferior properties when compared to the original chondral tissue, which may subsequently develop clinical osteoarthritis. Cartilage lesions are typically treated by condroplasty and palliative debridement techniques, drilling and microfracture repair, or restoration techniques that employ autologous chondrocyte implantation, mosaic arthroplasty and osteochondral allograft transplantation. Nevertheless, recent advances research on techniques to repair articular cartilage damage use a variety of transplanted cells or novel replacement devices, namely autologous chondrocytes and a wide range of scaffolds and cell-scaffold tissue engineering (TE) constructs colonized with cells from different origins, of which some of them have already been translated to human clinical application and, more recently, to gene therapy.

In this way, animal models of experimental articular cartilage defect are largely used in pre-clinical and translational research studies to assess novel concepts for chondral and osteochondral TE treatments aiming for regenerative joint resurfacing. Relatively to laboratory animal models, the large animal models (small ruminants – sheep and goat, pig, dog and horse) have the advantages of having joint size and cartilage thickness, and also the clinical lesions most similar to those present in humans. These large animal models also exhibit secondary Haversian bone tissue remodelling in the skeletally mature stages of their lifespan, bone tissue macro- and microstructure and composition, biochemical bone properties and bone mineral density more closely to humans. Nevertheless, there are variations in bone and cartilage tissues composition and mechanical properties that are species-dependent, being the most remarkable differences their rapid growth, with a predominance of plexiform or lamellar bone in the areas adjacent to the periosteum and endosteum of long bone cortices during the first years of their lifespan, and the quadruped locomotion relatively to the biped locomotion of the human species.

The ideal animal model should mimic as close as possible the clinical setting, being biologically analogous and recognizable as an appropriate model for cartilage physiology. Nonetheless, this objective of performing valid cartilage defect testing studies has been very difficult to achieve, since 95% of the human cartilage defects do not affect the subchondral bone. On the contrary, in experimental studies using animal models the subchondral bone is frequently involved with the subsequent advancement of the subchondral bone plate during spontaneous healing of osteochondral defects and following articular cartilage treatment for chondral lesions. Another difference between human cartilage lesions and those experimentally induced in animal models is the volume of the cartilage defect which is larger in humans than in animal models, having approximately a mean total volume of 552.25 mm^3, with 10 mm or more in diameter and usually involving only chondral tissue (Tab. 1). This fact could be partially justified by the large variation of cartilage thickness between human and the above referred animal species, where humans present the thickest articular cartilage at the stifle joint level (Tab. 1). Comparison of common currently used large animal models for articular cartilage repair.

Animal species	Joint(s)	Cartilage thickness (medial femoral condyle)	Defect type/size	Primary use	Post-operative management capabilities	Outcomes assessments
Sheep/ Goat	Knee	Sheep – 0.45 mm Goat – 1.1 mm	Surgically created 4-15 mm Mean total volume: sheep – 359.54 mm^3 goat – 251.65 mm^3 Chondral/osteochondral. Impact injury. CSD – 6-7 mm	Pivotal studies created defects for which post-operative management variables are not critical	Stall/pasture. Schroeder–Thomas splint	MRI, CT, X-ray. Subjective function. Gross. India ink staining. Histology. Biochemical. Biomechanical
Pig	Knee	1.5 mm	Surgically created 6-8 mm or larger Mean total volume: pig – 107.43 mm^3 Chondral/osteochondral. Impact injury. Osteochondritis dissecans. CSD – 6-6.3 mm	Pivotal studies created defects for which post-operative management variables are not critical	Stall/group housed	MRI, CT, X-ray. Subjective function. Gross. India ink staining. Histology. Biochemical. Biomechanical
Dog	Knee, shoulder, elbow, hip, ankle	0.95 mm	Surgically created 3-12 mm Mean total volume: dog – 82.39 mm^3 Chondral/osteochondral. Impact injury. Osteochondrosis. Secondary osteoarthritis. Elbow dysplasia CSD – 4 mm	Pivotal studies using surgically created or spontaneous defects; post-operative assessments and management most closely mimic human	Kennel/run/group housed. Bandages, casts, splints, orthotics, external skeletal fixators, non-weight-bearing slings. Dedicated exercice. Physical therapy	Arthroscopic scoring. MRI, CT, X-ray. VAS for pain, function, effusion and QoL. ROM. Muscle mass. Kinetics and kinematics. Gross. India ink staining. Histology. Biochemical. Biomechanical
Horse	Knee, carpus, ankle	1.75 mm	Surgically created 6-20 mm Mean total volume: horse – 334.73 mm^3 Chondral/osteochondral. Chip fracture. Osteochondrosis. CSD – 9 mm	Pivotal studies using surgically created or spontaneous defects; cartilage thickness and cartilage biomechanics most closely resemble human	Stall/pasture. Dedicated exercice	Arthroscopic scoring. MRI, and CT if special capabilities, X-ray. Subjective function. Kinetics and kinematics. Gross. India ink staining. Histology. Biochemical. Biomechanical

CSD – It should be considered the smallest wound established at the cartilage tissue, which cannot heal spontaneously during the lifetime of the animal.

Tab. 1. Comparison of common currently used large animal models for articular cartilage repair.

Consequently, the choice of an appropriate animal model for chondral or osteochondral TE studies should be based in published scientific literature and guideline documents of the American Society for Testing and Materials, the International Cartilage Repair Society and the United States Food and Drug Administration, performing a multifactorial analysis of each animal model (Tab. 1). These defects are generally focal surgically induced in large animal models and performed in the stifle joint at the condylar and trochlear femoral areas, where spontaneous regeneration should be excluded and the subchondral bone plate must be taken into consideration. Pilot studies for chondral and osteochondral bone TE could apply short observational periods for evaluation of the cartilage regeneration up to 12 weeks post-operatively, but generally a 6 to 12 months follow-up period is used for these types of studies. Depending on the particular treatment under research, the joint size, anatomy and arthroscopic access, usually favor the horse and the small ruminants, for articular cartilage repair studies.

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