

Stem cells in canine osteoarthritis. Part 2: case selection, choices, guidelines and outcomes

This article, which is part 2 of a 3-part series covering the use of stem cells in canine osteoarthritis, discusses case selection, intra-articular therapies, guidelines for joint injections and clinical metrology in the use of regenerative therapy techniques for osteoarthritis in dogs. Osteoarthritis is a prevalent condition in dogs, and can have a negative effect on quality of life. It is a chronic condition which requires long-term management, and stem cells are a potential method of improving quality of life in affected animals.

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Osteoarthritis is frequently seen in veterinary clinics, affecting up to 20% of dogs in the UK (based on referral data). In order to reduce the negative effects that this chronic condition can have on dogs that are experiencing it, research into using stem cells to benefit these dogs is ongoing. There are various ways that stem cell therapy can be applied to help these dogs; these are discussed in this article, which is part 2 of a 3-part series around the use of stem cells in canine osteoarthritis.

Practical uses of stem cell therapy in osteoarthritis

In practice, the most common uses of stem cell therapy in dogs are:

- As a primary or adjunctive intra-articular treatment for shoulder, elbow, carpus, hip, stifle, tarsus and interphalangeal joints once surgical intervention has been ruled out, often as part of a multimodal approach
- For tendinopathies: lesions of the biceps tendon, supraspinatus, subscapularis and medial glenohumeral ligament or 'medial shoulder syndrome' (Canapp et al, 2016a; García-Bernal et al, 2021), iliopsoas, gastrocnemius, patellar tendon and flexor carpi ulnaris in the dog have all been treated successfully with ultrasound guided stem cell injections

- For ligament repair: the use of stem cells in place of surgery for the treatment of anterior cruciate ligament repair where 50% or less of the ligament is damaged has been postulated (Linon et al, 2014; Canapp et al, 2016b). Currently, the recommended therapy for complete anterior cruciate ligament rupture is surgical correction (Mölsä et al, 2014).

Technique Diagnosis

Appropriate diagnostic techniques should be performed, and may include:

- Radiography
- Arthroscopy
- Ultrasonography
- Computed tomography
- Magnetic resonance imaging
- Synovial fluid analysis (cytology, culture and viscosity).

Training in the following modalities would be recommended:

- Small animal diagnostic musculoskeletal ultrasound
- Use of stance analyser and/or gait analyser
- Use of force plate analysis
- Use of goniometric measurements
- Diagnostic imaging for radiology +/- computed tomography scanning

- Intra-articular injections +/- ultrasound guided intra-articular injections.

Case selection for stem cell therapy

Patients are selected according to several criteria, and different clinicians will prefer one selection process over another. A 'candidacy check' process to determine suitability for treatment and maximise the potential for a successful outcome includes the study of previous clinical history, a specific series of owner-submitted videos of the patient and an in-depth consultation, as well as owner-derived osteoarthritis and quality of life scores.

Prospective patients are examined according to Canine Osteoarthritis Staging Tool guidelines and clinical staging. A multimodal approach is determined on a patient-by-patient basis, and on an individual joint basis, to include intra-articular therapies such as hyaluronic acid, platelet-rich plasma, autologous conditioned serum and polyacrylamide hydrogel alongside stem cell treatment where appropriate. In certain cases, intra-articular steroids (methylprednisolone or triamcinolone) may be indicated. It is also imperative to consider surgical vs medical management.

If the clinician is considering using regenerative medicine techniques for use in an affected joint, surgical management must be ruled out initially. An example of this might be in the treatment of elbow osteoarthritis where there is a concurrent fractured coronoid process, ununited anconeal process, osteochondrosis dissecans or a humeral condylar fissure requiring surgery. Regenerative intra-articular therapies may be used alongside surgical treatment, providing that the underlying surgical condition is addressed. Therefore, clinicians should rule out and consider surgical options in early onset joint disease, including:

- Hip: triple or double pelvic osteotomy, juvenile pubic symphysiodesis
- Cruciate disease: tibial plateau levelling/tibial tuberosity advancement
- Elbow dysplasia: osteotomy techniques to reduce load on the medial compartment
- Ulna: proximal ulna osteotomy and proximal ulna abducting osteotomy
- Humerus: closing wedge osteotomy and sliding humeral osteotomy
- Canine uni compartmental elbow prosthesis. Options for later or chronic disease include:
- Excision arthroplasty of hip
- Arthrodesis of tarsus, shoulder and carpus (elbow and stifle less commonly)
- Total joint replacement of hip (elbow, shoulder, stifle and tarsus less commonly)

Infectious arthritis and non-infectious erosive and non-erosive immune mediated disease, neoplasia, acute trauma and haemarthrosis must also be considered and ruled out.

Preconditioning the joint environment

It has been proposed that the effects of mesenchymal stem cells are compromised in an inflammatory environment.

Since most of the joints considered for treatment with mesenchymal stem cells provide an inflammatory environment, intra-articular treatment with platelet-rich plasma, autologous conditioned serum or autologous protein solution at an interval before introduction of mesenchymal stem cells may be beneficial in terms of efficacy and outcome (Vilar et al, 2013; Yun et al, 2016; Blázquez et al, 2019).

Autologous-conditioned serum is produced by incubating whole blood with borosilicate glass beads. It was investigated as a biological treatment for osteoarthritis because of an increased concentration of interleukin-1 receptor antagonist, a protein that is a competitive antagonist of the main inflammatory cytokine of osteoarthritis (interleukin-1-beta), as well as increased presence of anti-inflammatory cytokines interleukin-10 and interleukin-4.

Platelet-rich plasma is the plasma portion of the patient's own blood that has an increased concentration of platelets through centrifugation or filtration steps. There is an apparent concentration/benefit plateau and controversy over what exact fold increase in platelet count is most beneficial in osteoarthritis. As such, specific guidelines for equine or canine platelet-rich plasma have not been set, and may differ between tendinopathy and osteoarthritis. In one study, dogs with osteoarthritis were given a single intra-articular platelet-rich plasma treatment (3-fold increase in platelet count) that resulted in decreased objective and subjective lameness and comfort scores compared with baseline and placebo controls (Fahie et al, 2013).

Different commercially-available systems provide differing concentrations of platelets (Carr et al, 2016). Red and white blood cell counts have also been reported to affect the clinical efficacy of platelet-rich plasma, so multiple formulations of platelet-rich plasma have been developed and studied. Previous studies in humans have reported that the ideal platelet-rich plasma product should have anywhere from a 4- to 7-fold increase in platelets (McLellan and Plevin, 2011; Hsu et al, 2013; Pelletier et al, 2013).

Sample harvesting

Adipose tissue is collected from various sites according to the surgeon's preference, but primarily either from a subcutaneous site just caudal to the scapula (ideally on an unaffected limb), from falciform fat or (in the case of a patient with little subcutaneous or falciform fat) from omental fat under general anaesthesia. Use of subcutaneous fat in dogs can lead to seroma formation and may not provide an adequate sample. Depending on the processing technique, 10–15 g of adipose tissue is sufficient. Bone marrow is collected from the proximal humerus according to a standard technique.

Effect of patient age on stem cell harvesting

A study of 52 dogs to evaluate whether a dog's age influences either the growth rate of autologous adipose-derived mesenchymal stem cells during culture-expansion,

or clinical efficacy outcomes following treatment with intra-articular adipose-derived mesenchymal stem cell injections found that the patient’s age did not adversely affect the ability to culture the cells or impact clinical efficacy (Miller et al, 2018).

Stem cell processing

Processing harvested adipose or bone marrow aspirate may be carried out in two ways:

- Patient-side, where the stromal vascular fraction is obtained for injection into the affected area/joint, or patient-side where the bone marrow aspirate concentrate is processed for injection into the affected area or joint
- At an onsite or external Veterinary Medicines Directorate-approved laboratory where the stem cells are cultured. Choice of laboratory should include a consideration of geographical proximity and ability to courier samples in a timely manner. The veterinary surgeon should contact the laboratory they wish to use to process the stem cells before the procedure to:
 - Receive any training for the procedures necessary to obtain the samples
 - Ascertain what samples will be required for a specific case

- Obtain any necessary equipment for the procedures or transport of the samples.

Stem cell implantation

When cells are ready for implantation (either same day patient-side for bone marrow aspirate concentrate or stromal vascular fraction, or 2–4 weeks for culture techniques), the patient undergoes sedation or general anaesthesia, and the joint or joints are prepared for sterile intra-articular injections. Approaches to joints for intra-articular injections have been well described elsewhere, and training is recommended for intra-articular injection techniques. Intra-articular injections may be ultrasound guided and/or carried out using anatomical landmarks, and Table 1 describes general guidelines for the sites and volumes when injecting canine joints. Before injection of any intra-articular therapy, arthrocentesis should be carried out to ensure needle placement and assess viscosity and gross appearance of synovial fluid. Synovial fluid samples may be submitted for cytology and culture as necessary.

Combination therapy

As well as preconditioning the joint(s) with platelet-rich plasma, it has been postulated that combining adipose-

Table 1. General guidelines for canine joint injections, sites and volumes		
Joint	Guidelines	Total injection volume according to dog weight
Shoulder	● Recommended needle: 22 gauge, 1.5" ● Syringe for aspirating synovial fluid: 5 ml ● Landmark for blind injection: acromion process	Miniature (<5 kg): 0.5 ml Small (5–12 kg): 0.5–1 ml Medium (12–25 kg): 1–1.5 ml Large (25–50 kg): 1.5–2 ml Giant (>50 kg): 2–3 ml
Elbow	● Recommended needle: 22 gauge, 1.5" ● Syringe for aspirating synovial fluid: 5 ml ● Landmark for blind injection: medial epicondyle process	Miniature (<5 kg): 0.25–0.5 ml Small (5–12 kg): 0.5–1 ml Medium (12–25 kg): 1–1.5 ml Large (25–50 kg): 1.5–2 ml Giant (>50 kg): 2–2.5 ml
Carpus	● Recommended needle: 22 gauge, 1" ● Syringe for aspirating synovial fluid: 2 ml ● Landmark for blind injection: antebrachial carpal joint	Miniature (<5 kg): 0.25 ml Small (5–12 kg): 0.25–0.5 ml Medium (12–25 kg): 0.25–1 ml Large (25–50 kg): 0.75–1 ml Giant (>50 kg): 1 ml
Hip	● Recommended needle: 22 gauge, 1.5" or 2.5–3" spinal needle for larger dogs ● Syringe for aspirating synovial fluid: 5 ml ● Landmark for blind injection: greater trochanter, apply traction and external rotation to open joint space	Miniature (<5 kg): 0.5 ml Small (5–12 kg): 0.5–1 ml Medium (12–25 kg): 1–1.5 ml Large (25–50 kg): 1.5–2 ml Giant (>50 kg): 2–3 ml
Stifle	● Recommended needle: 22 gauge, 1.5" ● Syringe for aspirating synovial fluid: 5 ml. ● Landmark for blind injection: lateral to patellar tendon	Miniature (<5 kg): 0.5 ml Small (5–12 kg): 0.5–1 ml Medium (12–25 kg): 1–1.5 ml Large (25–50 kg): 1.5–2 ml Giant (>50 kg): 2–3 ml
Tarsus	● Recommended needle: 22 gauge, 1" ● Syringe for aspirating synovial fluid: 2 ml ● Landmark for blind injection: medial joint compartment	Miniature (<5 kg): 0.25 ml Small (5–12 kg): 0.25–0.5 ml Medium (12–25 kg): 0.25–1 ml Large (25–50 kg): 0.75–1 ml Giant (>50 kg): 1 ml

derived stem cell therapy with intra-articular platelet-rich plasma may be useful. Studies have shown that combining platelet-rich plasma and stem cells can have a synergistic effect on osteoarthritis via extracellular matrix synthesis and chondrocyte proliferation as well as via an anti-inflammatory mechanism. This combination of mesenchymal stem cells and platelet-rich plasma may be very useful as an inflammatory regulator for the treatment of osteoarthritis (Upchurch et al, 2016; Yun et al, 2016). On this basis, platelet-rich plasma and adipose-derived stem cells may be given intra-articularly at the same time depending on case selection and staging. It is currently not recommended to use intra-articular polyacrylamide gel concurrently with intra-articular adipose-derived stem cells until further evidence of the efficacy of adipose-derived stem cells in this media is available.

Diagnostic imaging

Radiographic changes may be useful in some cases, but they are generally slow for short time frames (Skangals, 2022). Any reliance on radiographic changes should include a recognised osteoarthritis scoring system or method of lesion measurement, eg the International Elbow Working Group, which uses a grading system to diagnose canine elbow dysplasia (DeLuke et al, 2012; Ondreka, 2015).

Computed tomography and magnetic resonance imaging are useful in documenting and monitoring changes in osteoarthritis, and consideration should be given to their relative appropriateness for the condition being treated. For example, computed tomography imaging shows many aspects of bony detail better than magnetic resonance imaging, while magnetic resonance imaging is more sensitive to soft tissue change and contrast resolution.

In two studies, no radiographic osteoarthritis progression was detected after intra-articular application of autologous and allogeneic adipose tissue-derived mesenchymal stem cells (Mohoric et al, 2016; Wits et al, 2020). A study applying autologous adipose tissue-derived mesenchymal stem cells in combination with hyaluronic acid and patellar luxation surgery described a decrease in osteophytes and subchondral cystic lesions on radiographic evaluation (Yoon et al, 2012). Based on radiographic and computed tomography imaging, therapeutically-administered mesenchymal stem cells are likely unable to reverse osteoarthritis-related bone changes

but may be able to slow down or even stop radiographic progression.

Musculoskeletal ultrasound can evaluate muscles, tendons, ligaments and intra-articular structures; training in musculoskeletal ultrasound techniques is recommended. Arthroscopy is minimally invasive and may be used for diagnostic imaging where direct visualisation and diagnosis of articular cartilage and soft tissue damage may be helpful, eg in cases of elbow dysplasia.

Measuring outcomes

In a general practice setting, clinical outcomes are ordinarily assessed via repeat clinical examinations, owner-reported history, monitoring of clinical signs, and monitoring of diagnostic tests and imaging where appropriate. In a setting specifically tailored to managing osteoarthritis, clinical outcomes may be divided into three main categories, each with several measures (Table 2).

Clinical metrics can be classed as subjective measures, validated subjective measures and objective measures. Owner history reporting and veterinarian interpretation, as well as physical examination, while instrumental to assessment and diagnosis of osteoarthritis and its effect on quality of life, are considered subjective by the author.

The clinician may find it useful to view the patient from a variety of angles and paces in a relaxed, familiar environment. The clinician can request a series of videos from the owner, to allow viewing of the patient from left and right sides, from behind and in front and free running off lead, as well as going up and down steps. Videos should show the dog moving on a hard flat surface like a pavement or a driveway to allow better visual assessment of gait and lameness.

Client-reported outcome measures include clinical metrology instrument questionnaires and health-related quality of life scores. Owners are asked to fill out a short questionnaire which gives the clinician a validated score or number. Scores can be reviewed at pre and post treatment intervals of several timeframes. The difference in pre and post treatment results are then related to a statistically significant minimal clinically important difference for each questionnaire type, which is the smallest difference in a score that owners perceive as beneficial. If the minimal

Table 2. Categories used to measure clinical outcomes

Subjective	Validated subjective	Objective
- Owner history - Veterinary clinical examination - Videos pre and post treatment	- Clinical metrology instrument questionnaires eg Liverpool Osteoarthritis in Dogs score, Texas visual analogue scale, canine orthopaedic index - Osteoarthritis pain scores eg the canine brief pain inventory, Helsinki chronic pain index, Hudson visual analogue scale - Health-related quality of life score eg Vetmetrica, Glasgow University veterinary school questionnaire - Osteoarthritis staging chart	- Diagnostic imaging: computed tomography, magnetic resonance imaging, radiography, musculoskeletal ultrasound - Stance analysis - Force plate analysis - Gait analysis - Activity monitors - Muscle circumference measurements - Goniometry range of motion measurements - Ability to reduce osteoarthritis medication

clinically important difference is achieved, the clinician can use this as a validated objective measurement to assess that a beneficial effect of the treatment provided has been achieved. Accuracy of results may be compromised because of the potential for an owner-related placebo effect (ie the owner wants to see a beneficial outcome).

The Liverpool Osteoarthritis in Dogs score is an owner-completed clinical metrology instrument that can be recommended for the measurement of canine osteoarthritis. It is convenient to use, validated and has a correlation with force-platform data. The Liverpool Osteoarthritis in Dogs clinical metrology instrument has been validated in dogs with chronic elbow osteoarthritis (Walton et al, 2013).

The canine orthopaedic index is an owner-completed outcome assessment instrument for dogs with orthopaedic disease (Brown, 2014). The Texas visual analogue scale is repeatable and valid for use in assessing the degree of mild to moderate lameness in dogs, as is the Hudson visual analogue scale (Hudson et al, 2004). The canine brief pain inventory allows owners to rate the severity of their dog's pain and the degree to which that pain interferes with function (Brown et al, 2008). It has been used to evaluate improvements in pain scores in dogs with osteoarthritis and in dogs with osteosarcoma. The Helsinki chronic pain index provides a valid, reliable and responsive tool for assessment of response to treatment in dogs with osteoarthritis (Hielm-Björkman et al, 2009). The Liverpool Osteoarthritis in Dogs score, canine brief pain index and Helsinki chronic pain index have been measured against objective peak vertical force and show significant correlation (Walton et al, 2013).

Quality of life

Health-related quality of life tools measure the emotional as well as the physical impact of osteoarthritis (Reid, 2024). The Glasgow University veterinary school questionnaire is an owner-based questionnaire developed using psychometric principles for assessing the impact of chronic pain on the health-related quality of life of dogs and is validated in dogs with joint disease and cancer. It is a valid and reliable companion animal health-related quality of life instrument, presented in a web-based format, with automated production of a health-related quality of life profile. It offers major advantages to dog owners, practitioners and researchers (Reid et al, 2013).

Vetmetrica offers a valuable tool in assessing the impact of chronic pain on quality of life in dogs and cats. The questionnaire consists of 22 questions and is completed quickly and easily online by the owner and the resulting quality of life profile across four domains (energy, happiness, comfort and calmness) can be compared with that of age-matched healthy dogs (Wiseman-Orr et al, 2006; Davies et al, 2019).

Osteoarthritis staging

Several methods for staging the clinical state of osteoarthritis in dogs have been described, including the AIM-OA multimodal system (AIM OA, 2024) and a 5-stage grading

system described by Canine Arthritis Management (2024). Staging is important in osteoarthritis to define treatment options and assess treatment response.

Stance analysis

Stance analysis determines weight distribution while a dog stands on a pressure plate, whereby it is observed that a dog will offload a painful limb and redistribute weight to other limbs to compensate. One such device is the companion stance analyser. Normal weight distribution in a dog is defined as 30% in each forelimb and 20% percent in each hindlimb (Clough et al, 2018). Stance analysis may be used to compare weight distribution at pre and post treatment intervals, and the author also finds it useful as part of an orthopaedic examination, particularly when multiple limbs are affected by osteoarthritis (Clough et al, 2018; Skangals, 2022).

Force plate analysis and kinetic gait analysis

Force plate analysis is a common method for measuring ground reaction force in dogs (Budsberg et al, 1987) and can be used to assess lameness and osteoarthritis. Ground reaction forces have been extensively used in dogs to gain insights on normal locomotion, discrepancies under pathological conditions and biomechanical changes following surgical procedures, and have become a well-established outcome measure of pain-related functional impairment in animals affected by experimental and naturally-occurring osteoarthritis (Moreau et al, 2014). A force plate is a computerised sensor plate mounted on the floor that measures the forces a dog generates when it steps. The forces are measured in three dimensions: vertical, craniocaudal and mediolateral. Force plate analysis can measure a variety of parameters, including:

- Peak vertical force: the largest force generated during the stance phase
- Vertical impulse: the area under the vertical force curve
- Symmetry index: the ratio of the difference between the left and right ground reaction forces to the average of the left and right ground reaction forces.

Force plate analysis can help detect lameness and provide insight into the mechanical processes of locomotion and has been compared to the canine brief pain index for the assessment of osteoarthritis in dogs (Brown et al, 2013).

Gait analysis (eg Canid gait; Zevris) uses a pressure sensitive treadmill that measures a range of parameters including step length, step width, stride length and swing phase measurements. Kinematic gait analysis quantifies the positions, velocities, acceleration/deceleration and angles of various anatomic structures in space. Most kinematic gait analysis systems use coloured, retroreflective, or LED markers that identify specific anatomic landmarks.

Canine activity wearables can be used before treatment starts to monitor exercise and daily activity before, during and after treatment (Kujala et al, 2024). Information can be shared from an app to the clinician, providing valuable data that may reflect willingness to exercise and changes in mobility and

pain. Muscle circumference measurements using callipers or tape may be useful in limbs that are offloaded as a result of musculoskeletal disease, and while some work has been done to establish standard measurements and ratios (Fox et al, 2023), the author suggests using these to measure trends in an individual patient.

Goniometry for range of motion

The range of motion of treated joints can be measured before and after stem cell treatments, and normal range of motion has been established for several breeds (Jaegger et al, 2002; Sabanci and Ocal, 2016; Thomovsky et al, 2016; Formenton et al, 2019). A goniometer can be used to measure flexion and extension of an individual joint. Anatomical landmarks for goniometer placement and images of correct placement have been published (Jaegger et al, 2002; Armitage et al, 2023); essentially, the pivot point of the goniometer is placed over the centre of motion of the joint and its arms aligned along the proximal and distal bone axes. The proximal arm of the goniometer is held in place whilst the joint is fully flexed and extended. Range of motion is calculated by subtracting the flexion angle from the extension angle.

The assumption is that for a joint to gain a greater total range of motion, there must be some combination of bone remodelling, a change in joint capsule thickness or elasticity or a change in muscle-tendon length, which was previously restricting flexion or extension. However, it is important to consider changes in environmental temperature, chronological proximity to exercise and rest, and the presence or absence of joint effusion when interpreting these data. The effect of pain or anticipation of pain in a conscious dog which may limit flexion or extension compared to measurements taken in a sedated or anaesthetised dog (Clarke et al, 2020) should also be considered. Studies using range of motion as an objective measurement for treatment of osteoarthritis have been performed (Skangals, 2022; Armitage et al, 2023).

The requirement for anti-inflammatory and analgesic medication to maintain mobility, reduce pain and improve quality of life may be used as an objective measurement of the effectiveness of stem cell therapy. One of the proposed benefits of adipose-derived stem cell therapy is that it may reduce the need for pharmaceutical intervention, which may in turn reduce long-term costs for owners and be beneficial for patients who cannot tolerate medication or for whom compliance is poor.

Conclusions

Stem cell therapy has become a valuable component in the management of canine osteoarthritis, providing anti-inflammatory effects, promoting tissue repair and improving joint function. Proper diagnosis through imaging and clinical assessment is crucial for case selection, ensuring that surgical alternatives are considered where appropriate. Effective preconditioning of the joint environment, including with platelet-rich plasma or

KEY POINTS

- Stem cell therapy is an effective option for canine osteoarthritis, offering anti-inflammatory benefits, promoting tissue repair and improving joint function, particularly when used as part of a multimodal treatment plan.
- Proper diagnosis and case selection are crucial. Imaging techniques help determine suitability, and surgical alternatives must be considered before opting for regenerative therapy.
- Preconditioning the joint environment enhances treatment efficacy.
- Different sample harvesting and processing methods impact treatment success.
- Objective outcome measurement is essential – clinical success should be assessed to track progress and refine treatment approaches.

autologous conditioned serum, may enhance stem cell efficacy. Sample harvesting and processing methods, whether patient-side or laboratory-based, influence treatment success, while precise stem cell implantation techniques optimise therapeutic outcomes. Combination therapies, such as platelet-rich plasma with stem cells, show promise in improving efficacy. Outcome measurement, including gait analysis, force plate assessment and validated pain scoring is essential for tracking treatment success. Current evidence supports stem cell therapy as a viable and integrative option for improving mobility and quality of life in dogs with osteoarthritis. **CA**

Conflicts of interest

The author declares that there are no conflicts of interest.

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