EXPERIMENTAL OSTEOARTHRITIS MODELS IN VETERINARY MEDICINE – RELEVANCE, POTENTIAL AND CHALLENGES

N. V. GORANOV

Department of Veterinary Surgery, Faculty of Veterinary Medicine,
Stara Zagora, Bulgaria

Summary


The aim of the present review is to summarise, classify and outline the benefits and disadvantages of the models for reproducing osteoarthritis, most commonly used in experimental veterinary orthopaedics (spontaneous, chemical and physical). The potential for application of a given experimental model is related to its specific research target – evaluation of pain, role of inflammation, sex, age, motility and overweight, as well as provision of a solid background for testing of modern pharmacological and physical means of disease control. With this regard, the experimental reproduction of osteoarthritis does not focus on model unification, but is a scientific and practical field developing towards broadening and revealing new heuristic and clinical diagnostic horizons related to improving the quality of life in both human and animal patients with osteoarthritis.

Key words: experimental model, osteoarthritis, review

INTRODUCTION


The experimental reproduction of a specific disease is always of substantial scientific and practical importance. Very often, this is the only way to confirm a working hypothesis. The experimental in vivo models in different animal species are successfully used for a long time in human and veterinary medicine to investigate the immunological, histological and biochemical pathways of the disease, to test different diagnostic approaches, operative techniques and drugs.

Orthopaedics is a field where experimental models are intensively used (Bendele, 2001; Murray, 2002). Many of veterinary surgery accomplishments related to osteoarthritis control are due to such models. Researchers in the field of human osteoarthritis also use animal models, due to ethical issues (Lascelles & Flecknell, 2010).

Bentley (1974); Little & Smith (2008) have summarized the general characteristics of an osteoarthritis model:
- Initial loss of matrix and progressive cartilage erosion.
- Reproducibility of articular cartilage changes.
- Lack of reactions in adjacent extra-articular structures.
- Lack of systemic effect.
- Common to different animal species, especially mammals.
- Prediction of development.

Such an ideal model does not really exist. It is very difficult to reproduce all disorders and symptoms of OA due to its occult and indistinct beginning, yet multiple attempts have been made. Conceptually acceptable is the model that possesses the most important attributes of natural disease and that could be reproduced (Brandt, 2002; Carlson, 2005). This type of modelling has the advantage that after the experimental animals have developed symptoms similar to the natural disease, they could be treated without being necessarily euthanized, regardless of the research purpose.

The interest towards experimental models of OA on the knee joints is arising from its anatomic features and the high prevalence of natural degenerative events (Bendele, 2001; Carlson, 2005).

The large variety of existing models has been classified (with some variations) by Witter (1999) and Schaller et al. (2005) as spontaneous (natural), ovariectomy, chemical and physical (biomechanical).

**SPONTANEOUS OSTEOARTHRITIS MODELS**

Their major advantage is the totally natural occurrence and development of disease, without any direct intervention or stimulation.

**Genetic selection**

It was established that the incidence of degenerative changes occurring without a specific artificial stimulus, was considerably higher in some breeds of dogs and rabbits and therefore, they are purposefully bred. A disadvantage of this approach is the slow development (years) of the degeneration (Hoegh-Andersen et al. 2004; Carlson et al. 2005) and the impossibility to identify the moment OA started to develop (Schaller et al. 2005; Witter, 1999).

**Alimentary-induced obesity**

A high-fat diet fed to mice from the 9th to the 54th week of life, resulted in increased incidence of osteoarthritic changes, especially of the knee joint (Griffin et al., 2010). Moreover, these findings were due not to obesity in general (respectively the biochemical overload) but also to adipose-associated inflammation caused by high blood concentrations of leptin, adipokines, adiponectins and interleukin-1α. These levels correlated with the severity of alterations in cartilage extracellular matrix.

**HORMONE DEFICIENCY MODEL OF OSTEOARTHRITIS**

**Ovariectomy**

The surgical removal of ovaries produces a systemic metabolic hormonal imbalance, which indirectly influences the joint integrity and health. The model is used in mice, rats (Bendele, 2001) and monkeys (Ham et al. 2002). The occurring oestrogen deficiency after ovariectomy results in degenerative alterations of joint cartilage and bones similar to early human osteoarthritis (Schaller et al., 2005). Thus, it is possible to investigate
the effect of gender upon the prevalence and severity of disease, but it is not clear whether this physiological deficiency could be differentiated from the naturally occurring aging.

CHEMICAL MODELS OF OSTEOARTHRITIS

Multiple substances applied intraarticularly could provoke initial rapid (for hours) inflammation, cytotoxic and at a later stage, structural cartilage damage. The concentrations of oxidative stress parameters and the activity of a number of enzymes are markedly changed (Al-Saffar et al., 2011). The reproduction of a rapidly developing synovitis is useful for investigation of pain and motility, which are the earliest osteoarthritic changes and could remain undetected in animal patients. In such instances, the net effect of one or another non-steroid or steroid anti-inflammatory drug could be tested. As the degenerative changes in the early stage of OA are not severe, such models possess the advantage of being reversible, although within a narrow time interval. It should be mentioned that apart being of interest for experimental orthopaedics, the systemic effects of used chemical agents are not well investigated.

Direct cartilage degradation models

It is a challenge using organic substances, which, after intraarticular injection could attack cartilage directly, without a systemic toxic effect – natural enzymes, mediators of inflammation (collagenases, metalloproteinases, cytokines) (Van der Kraan et al. 1990), 10% sodium chloride (Vasilev et al. 1992), vitamin A (Lapadula et al.1995), papain (Kitoh et al., 1992), turpentine oil and gentamicin (Singh et al., 1997), the antibiotic filipin (McIlwraith et al., 1981), sodium urate (Bonneau et al., 2005) etc. Such models are potentially dangerous as the inflammatory, which is extremely strong, could not be controlled within the target intraarticular structures and finally, a plegmonous-necrotic outcome would be rather attained than a degenerative arthrosis process.

Indirect cartilage metabolism inhibition models

These are the most preferred from the group of chemical OA models. The metabolic inhibitor sodium monooiodoacetate (MIA) destroys indirectly the articular cartilage by inhibition of glyceraldehyde-3-phosphate dehydrogenase in chondrocytes, interrupting the glycolysis pathway. The rapid adenosine triphosphate consumption results in energy depletion and cell death. Thus, the number of chondrocytes decreases progressively, and subsequently, the synthesis of proteoglycan components for the cartilage matrix stops (Kalbhen, 1987; Van der Kraan et al. 1989). Over 6–8 weeks, a degenerative process typical for natural osteoarthritis in humans and animals does occur (Kalbhen & Blum, 1977; Janusz et al., 2001; Guzman et al., 2003).

The reported times of occurrence of changes are very different, as well as the used MIA doses and the number of intraarticular applications. Fourteen weeks after two intraarticular MIA injections (0.6 mg) in the knee joints, Kalbhen & Jansen (1990) detected radiological and pathoanatomical changes in chickens. Gencosmanoglu et al. (2001) have achieved a chondrotoxic effect in rats after 8 weekly injections of 1 mg MIA. Permanent proteoglycan content changes and histological signs were reported 2 to 8 weeks after application of 1–3 mg MIA in rats. They were progressive and similar to
OA lesions in humans (Saied et al. 1997; Guinamp et al. 1997; Bovine et al. 2003; Guzman et al. 2003). The rat model with administration of 2 mg MIA was used to evaluate chronic joint pain over 10 weeks (Combe et al. 2004). In mice, Boileau et al. (2004) have used a single dose of 0.1 mg MIA and reported histological changes 7–14 days later.

In rabbits, the described events occurred until the 12th week (Horn et al. 1988; Regling et al. 1989). In horses, Gustafson et al. (1992) have evaluated the changes in carpal joints with regard to the applied MIA dose after 12 weeks as mild (0.09 mg/kg), moderate (0.12 mg/kg), and severe (0.16 mg/kg). It was also found out that high intraarticular MIA doses (60–100 mg/mL in 2 mL) provoked a chemical arthrodesis of equine tarsal joint after 13–51 months (Bohanon, 1995; Penraat et al. 2000). In a dog model, Stobie et al. (1994) attempted to reproduce OA by applying two doses of MIA (0.375 mg/kg and 0.500 mg/kg) at a 2-week interval, but achieved only an insignificant lameness without permanently affected locomotion and biochemical profile until the 12th post injection week. The study was not supported with histological evidence, but nevertheless it was suggested that higher doses and/or multiple injections would result in more consistent OA changes in this animal species. Goranov & Vidinov (2005) have applied MIA in the knee joint of dogs once weekly at increasing doses of 0.12, 0.14, 0.16, 0.26, 0.36, 0.96, 1.28, 3.00, 5.00 and 10.00 mg/kg in 1 mL saline and by scanning electron microscopy showed that the monoiodoacetate model of osteoarthritis could be reproduced in dogs. The observed changes were consistent with those observed in other mammalian species. Therefore, the substance dose and the number of applications were essential with regard to the successful model reproduction.

This model, according to published reports, has demonstrated an unquestionable advantage – acknowledged and clear beginning, relatively rapid development, reproducibility and symptoms, typical for primary (idiopathic) osteoarthritis. So far, no data about systemic influences have been reported.

**PHYSICAL MODELS OF OSTEOARTHRITIS**

Physical or biomechanical models of OA are the most commonly used in human and veterinary orthopaedic research. They could reproduce sport traumatism in men and accidental traumas in dogs without using chemical substances to modify the metabolic pathways. A number of surgical interventions (desmotomy, meniscectomy, deliberate patellar contusion or luxation, continuous immobilization, non-physiological overload), are used to induce mechanical stress upon articular cartilage, impaired congruency, motility and joint instability. The deteriorated biomechanics further challenges the metabolism of chondrocytes and subchondral bone towards degeneration and reparation (Witter, 1999; Schaller et al., 2005).

**The Pond-Nuki model**

The rupture of ligaments is the most frequent natural cause of OA. The multiple investigations on the cranial cruciate ligament (CCL) of the knee do not explain all causes for its spontaneous rupture – in many cases, trauma is absent. Although opinions differ, the signs of OA are usually seen 3 to 5 weeks after CCL rupture and progress regardless of the therapy (conservative or surgery) (Vasseur, 1993).
The model with canine stifle surgical CCL resection proposed for the first time by Pond & Nuki (1973) is the most popular. It creates a mechanical instability resulting in progressive OA alterations in the dog, similar to those in men. The resection could be performed by percutaneous stab incision, open arthrotomy and arthroscopically guided transection, with most advantages being attributed to the last technique (Trumble et al., 2001). The morphological changes in bone, cartilage and synovial membrane in dogs occur within 16 weeks following a mechanism identical to natural osteoarthritis (McDevitt et al., 1977). Inflammatory changes of synovial fluid are reported up to the 90th day (De Biasi et al., 2001). Subchondral bone, submitted to focal alteration stress, changes its mineral density for 3–12 weeks (Boyd et al., 2000), the activity of metalloproteinases is markedly increased (Pelletier et al., 2002). Furthermore, the blood concentrations of oxidative stress parameters malondialdehyde and catalase were found to increase and to correlate with the increased blood collagen degradation products (Goranov, 2007).

The known and obvious onset of the degeneration is the reason why most researchers consider the Pond-Nuki model exceptionally appropriate for investigations of osteoarthritis in other animal species – sheep (Tappet et al., 2003), rats (Williams et al., 1985; Stoop et al., 2001) and rabbits (Hulth et al., 1970; Kaab et al., 1999).

**Immobilisation model**

Hamsters, immobilised for 3 months, have exhibited reduced proteoglycan content and lower synovial fluid volume in the stifle joint (Otterness et al., 1998). Haapala et al. (2001); Torelli et al. (2005) applied 12-week splint immobilisation of the stifle joint in rabbits. The cartilage metabolism showed symptoms of both degradation and synthesis, i.e. the process was reversible in these terms. Such a model would be useful for immunological assay of collagen metabolism markers, as the alterations in the cartilage in this model are mainly trophic.

**Groove model**

Another technique consisting in making grooves in the articular cartilage in areas with maximum load in dogs, is known as canine groove model. Degenerative changes were similar to those observed in the Pond-Nuki model, but developed over a considerably longer period (20–40 weeks) (Marijnissen et al. 2002). The changes reproduce the naturally occurring erosion in OA development with age, characterized by slow but steady progression of degenerative events with domination over the repair potential of the cartilage matrix.

**Mechanical overload model**

In another study, the mechanical overload of the hindlimb in dogs was reported to induce subchondral microfractures of the femoral condyle with onset of a typical degeneration of cartilage (Lahm et al. 2005). This way, the effect of overweight (obesity) in animals and humans as a factor for the wear and degeneration of joints could be investigated. In general, this model is intermediate between naturally occurring and biomechanical OA models.

**Hypermotility model**

The purpose of this model was to induce a physical wear of cartilage, which exceeds its normal capacity for physiological motility and repair. Pap et al. (1998) demonstrated the destructive effect of strenuous physical exercise on the joints.
of rats. Using intracranial self-stimulation, rats ran distances equal to 15 and 30 km within 3 and 6 weeks, respectively, in a running wheel. By the end of the trial, the activity of degradation enzymes (metallo-proteinases) was substantially increased. In a similar approach, horses which underwent a 19-week strenuous training programme, exhibited degenerative changes and chondrocyte loss from the superficial cartilage layer in loaded joints (Murray et al. 1999; Murray, 2002). An advantage of this model is that induced articular cartilage changes were identical to those occurring in elderly subjects, which otherwise could be hardly monitored due to prolonged development and comorbidity of various origin (metabolic, liver, hormonal, neurological) in such patients.

CONCLUSION

The variety of experimental models of osteoarthritis confirms the importance and the existing multidisciplinary interest to this disease. It turned out that a given model was not able to reproduce independently and completely all symptoms of this complex illness. Therefore, the wrong approach towards OA modelling would inevitably reflect on the significance of results. As long as in modern medicine OA is regarded as a chronic and irreversible disease, often leading to disability, it is clear that its experimental reproduction would focus on concepts related to improving the quality of life in animal and human patients, making experimental osteoarthritis research a mission of great social and economical impact. That is why, a well-grounded experimental design should carefully select a specific experimental model of osteoarthritis in the appropriate animal species according to the aims and terms of the research.

REFERENCES


Experimental osteoarthritis models in veterinary medicine – relevance, potential and challenges

Arthritis Research & Therapy, 6, R169–R180.


Janusz, M., S. Hookfin, S. Heimeyer, J. Woes1


Otterness, L., J. Eskra, M. Bliven, M. Shay, J. Pelletier & A. Milici, 1988. Exercise protects against articular cartilage degene-


Experimental osteoarthritis models in veterinary medicine – relevance, potential and challenges


Paper received 14.09.2011; accepted for publication 11.11.2011

Correspondence:

Dr. Nikolay V. Goranov, PhD
Department of Veterinary Surgery,
Faculty of Veterinary Medicine,
Student's Campus,
6000 Stara Zagora, Bulgaria