How to establish an expected animal model of post-traumatic osteoarthritis?

Peng-Fei Han a, b, 1, Cheng-Long Chen b, 1, Zhi Tian b, Peng-Cui Li b, Lei Wei b, Zhi Lv b, Xiao-Chun Wei b, *

a Department of Orthopedic Surgery, Second People’s Hospital of Changzhi City, Changzhi, Shanxi 046010, China
b Department of Orthopedic Surgery, Second Clinical Medical College, Shanxi Medical University, Taiyuan, Shanxi 030001, China

Abstract

Background: Animal models of osteoarthritis (OA), including post-traumatic osteoarthritis and spontaneous osteoarthritis, have been established in many ways. In recent years, there have been many reports in various foreign academic journals, but animal models of post-traumatic osteoarthritis (distinct from spontaneous osteoarthritis) have rarely been established or summarized in these reports. Animal models of post-traumatic osteoarthritis show different characteristics depending on the animal species and modeling methods used, which is why we have written this article.

Objective: To summarize the research progress and research status of animal models of post-traumatic osteoarthritis.

Methods: A retrospective review of the animal model of post-traumatic osteoarthritis (OA) was conducted on the basis of reports retrieved from the PubMed database with the keywords for searching "animal model, post-traumatic osteoarthritis (PTOA)" from October 2006 to October 2016 and confirmed English language. A total of 80 academic articles on the study of animal models of traumatic osteoarthritis were retrieved, and 34 of them were included in this literature review after reading the free full-text of them.

Results: Different PTOA models based on different modeling methods and different animal species had their own characteristics. Different modeling methods should be selected according to different modeling animals.

Conclusions: Considering the project funds, experimental objectives and technical conditions, appropriate experimental animal and modeling method should be selected based on synthetic considerations to obtain an appropriate PTOA model and ideal experimental results.

1. Introduction

Osteoarthritis (OA) is a common inflammatory joint disease that affects a growing portion of the elderly and has a strong socioeconomic impact.1 Because the pathogenesis and etiological factors of post-traumatic osteoarthritis are not clear, the lack of effective clinical diagnosis and treatment measures for the recovery of such patients has caused difficulties; therefore, it is necessary and urgent to study OA by establishing a traumatic osteoarthritis animal model.

Animal models of post-traumatic osteoarthritis can be established by selecting different animal species through a variety of artificial means to induce progressive cartilage injury, subchondral bone reconstruction, osteophyte formation and soft tissue inflammation around the joints and other pathological processes. In this review, we summarize the research methods and current research situation of animal models of post-traumatic osteoarthritis, covering nearly ten years of foreign academic papers, to provide appropriate reference methods for modeling post-traumatic osteoarthritis animal models in future studies.

2. Data and methods

2.1. Source

First, the authors searched the PubMed database from October 2006 to October 2016 for animal models of post-traumatic osteoarthritis using the keyword search of "animal model, post-
traumatic osteoarthritis (PTOA)” with an English language restriction.

2.2. Inclusion criteria

The eligible literature should describe the related experimental study work and summarize the establishment and use of animal models of post-traumatic osteoarthritis.

2.3. Exclusion criteria

The exclusion criteria were an unreasonable experimental design and experimental methods and poorly described or repetitive description of the establishment of animal models.

2.4. Quality control

According to the inclusion criteria and exclusion criteria, the first and second authors read the references carefully to obtain qualified literature.

2.5. Search results

A total of 80 academic papers studying animal models of post-traumatic osteoarthritis were retrieved, and 34 of them were included in this review after reading the free full-text articles.

3. Results

3.1. Extra-articular induction: tibial compression overload model (7/34)

In 2012, Christiansen et al\(^2\) used C57BL/6N mice and an overload cycle of the tibial compression method using a tibial compression system that consisted of two custom-built loading platens to establish a post-traumatic animal model. The bottom platen held the knee flexed, and the top platen positioned the foot with the ankle at approximately 30°. Then, the right leg of each mouse was subjected to a single dynamic axial compressive load, which caused a transient anterior subluxation of the tibia relative to the distal femur (Fig. 1). In view of the normal activities of the joint stress environment of articular cartilage, this modeling method is of great significance. Increasing or decreasing joint stress artificially could result in PTOA. Bone matrix damage is caused when stress artificially increases or decreases. Due to compensatory hypertrophy and degeneration of cartilage cells, cartilage degeneration of the entire animal cartilage joint occurs.

Satkunanathan et al\(^3\) used C57BL/6N mice to successfully replicate the PTOA model in their experiments. Killian et al\(^6\) successfully established a model by subjecting Flemish Giant rabbits to a blunt force insult to the tibiofemoral joint with compression axial overload. Tochigi et al\(^7\) successfully molded the elbow joint PTOA model using agricultural pigs. The elbow joints received an axial compression overload. Borrelli et al\(^8\) changed the position of the overload. New Zealand White rabbits received compression on the medial condyle of a femur to successfully simulate the course of human PTOA.

3.2. Intra-articular surgery

3.2.1. Anterior cruciate ligament transection, ACLT model (4/34)

In 1973, Pond et al\(^9\) performed anterior cruciate ligament transection surgery in one of the hind limb knees of 10 dogs, and the contralateral joints were used as controls. The animals were sacrificed at different times 1–26 weeks after surgery. Radiological and pathologic examinations showed that the humanoid PTOA model was successfully established (Fig. 2). This modeling principle generally indicates that the tibia should be constrained from the anterior cruciate ligament to limit its excessive movement. After the anterior cruciate ligament of the animal model was removed, forward displacement of the tibial and hind limb knee joint rotation inward increased the flexion and extension processes of the animal’s hind limb knee, resulting in joint stability destruction, eventually causing PTOA.

The canine ACLT model demonstrated that the animals recovered to a preoperative level 5 months after ACLT surgery by observing their ground reaction force (GRFs) and hind knee joint mechanics data. In 2005, Boyd et al\(^{10}\) divided 13 cats into three
groups and used the same ACTL method to mold the humanoid PTOA model to eliminate interference from the species variance in animal models. Then, they used Micro-CT to observe the long-term effects of bone around the joint (including the proximal tibia subchondral bone, femoral condyle and metaphyseal cancellous bone) and assess its effects in the pathogenesis of PTOA. Similarly, in 2014, Nagai et al.\textsuperscript{11} using Japanese White Rabbits and the ACTL technique to establish the rabbit PTOA model. In 2016, it was reported that Dong et al.\textsuperscript{12} successfully molded the mouse PTOA model and M\textsuperscript{99}/C\textsuperscript{19}evel et al.\textsuperscript{1} used New Zealand white rabbits to model the humanoid PTOA model. These authors obtained the expected experimental results.

3.2.2. Destabilization of the medial meniscus, DMM model (9/34)

In 1973, Moskowitz et al.\textsuperscript{13} divided 82 New Zealand white rabbits into three groups, the rabbits’ right hind limb knee was opened from the anterior medial side under aseptic conditions to expose the knee joint intermediate chamber, and then, the anterior half of the medial meniscus appendixes associated with 1/3 of the meniscus was removed. The humanoid PTOA model was established (Fig. 3). By contrast, Arunakul et al.\textsuperscript{14} used 16 New Zealand white rabbits to mold the PTOA model for use in the total meniscectomy (TMM) surgery method, resulting in instability of the medial meniscus of the animal knee. Similarly, Panahifar et al.\textsuperscript{15} applied the Medial Meniscectomy (MMx) technique to mold the humanoid PTOA model for use in Sprague-Dawley rats.

The modeling process of the DMM model takes longer time than the ACTL model mentioned previously.\textsuperscript{16,17} In their 2007 report, Glasson et al.\textsuperscript{18} used ADAMTS-4 and ADAMTS-5 gene knockout mice to compare the ACTL model and DMM model by evaluating the degree of cartilage damage with a histological scoring system. It was concluded that the ACTL model was able to mimic the severer
human PTOA process, in which some ACTL animals show serious hind subchondral bone erosion and osteophyte formation in the tibial plateau. By contrast, the DMM model has less invasion; the tibial plateau and middle of the femoral condyle only demonstrate mild damage; therefore, Glasson et al. believe that DMM is the preferable operational method choice for mouse PTOA modeling. Usmani et al. all adopted the above-mentioned viewpoint in the molding method in their experiments and successfully developed the murine PTOA model.

### 3.2.3. Hulth model/modiﬁed Hulth model (4/34)

According to the article "Experimental osteoarthritis in rabbits. Preliminary report" in 1970, Hulth and others removed the anterior cruciate ligament and medial collateral ligament, completely removed the medial meniscus using an experiment on rabbits, and successfully molded the humanoid PTOA model. The histological observation showed that the characteristics of PTOA, such as cartilage surface cracks and damage on the cartilage surface, were observed 3 months after Hulth’s surgery (Fig. 4). Hulth’s surgery destroyed the main ligaments (including the anterior cruciate ligament and medial collateral ligament) that maintain the static stability of the knee joint of the animal. As a result, the normal force line of the knee changed from eversion of $10^\circ$ to varus, and the axial pressure of the joint changed, with the normal lateral tibial plateau moving to the medial side so that the weight-bearing surface of the joint decreased. In addition, the stress concentration increased the local articular cartilage compression, resulting in joint stability damage and aggravating articular surface wear as well as using other surgical techniques to simulate the human PTOA process. However, we found that in the long term, the PTOA performance will still appear in some patients, even if their cruciate ligament has been reconstructed and they already have a relatively stable joint structure. To better understand and explore the pathogenesis of PTOA, Heard and others conducted an experiment on sheep using the autologous ligament graft autograft reconstruction method after anterior cruciate ligament surgery and eventually molded the humanoid PTOA model. Increased matrix metalloproteinases as well as interleukin-like PTOA inflammatory markers could be observed in joint fluid 2 weeks after surgery (Fig. 5).

This model has eliminated the influence of the instability of the joint structure on the incidence of PTOA, so we can fully understand the inflammatory factors and early catabolic effects on the onset of PTOA, providing sufﬁcient time to address the drug treatment window; therefore, the authors of this paper believe that this model is superior to the previous model, and we can regard this model as an idealized large animal model for the early diagnosis and treatment of PTOA (especially for studies of inflammatory factors and catabolic mechanisms).

### 3.2.4. Anterior cruciate ligament (ACL) auto graft anatomic reconstruction, ACL-R model (1/34)

In view of the above-mentioned various modeling methods, all of the methods focus on the joint instability pathway by destroying the joint stability structure and aggravating articular surface wear as well as using other surgical techniques to simulate the human PTOA process. However, we found that in the long term, the PTOA performance will still appear in some patients, even if their cruciate ligament has been reconstructed and they already have a relatively stable joint structure. To better understand and explore the pathogenesis of PTOA, Heard and others conducted an experiment on sheep using the autologous ligament graft autograft reconstruction method after anterior cruciate ligament surgery and eventually molded the humanoid PTOA model. Increased matrix metalloproteinases as well as interleukin-like PTOA inflammatory markers could be observed in joint fluid 2 weeks after surgery (Fig. 5).

This model has eliminated the influence of the instability of the joint structure on the incidence of PTOA, so we can fully understand the inflammatory factors and early catabolic effects on the onset of PTOA, providing sufﬁcient time to address the drug treatment window; therefore, the authors of this paper believe that this model is superior to the previous model, and we can regard this model as an idealized large animal model for the early diagnosis and treatment of PTOA (especially for studies of inflammatory factors and catabolic mechanisms).

### 3.2.5. Intra-articular fracture (IAF) model (3/34)

Goetz et al. used Yucatan miniature pigs to simulate the pathogenic course of PTOA using a special tripod ﬁxation, using immobilization after a tibial osteotomy of 1–2 mm of the pig knee (Fig. 6). Lewis et al. used C57BL/6 mice to mold a humanoid...
PTOA model using the artificial compression axial overload method to cause an animal tibial plate fracture. Due to equipment limitations (such as a special tripod and compression table) and the corresponding internal fixation materials, the authors do not recommend this method of establishing the models.

4. Discussion

In summary, after a retrospective review of the animal model of post-traumatic osteoarthritis in the PubMed database, it was determined that there are a variety of methods to model post-traumatic osteoarthritis (mainly in the knee) by using animal model, and the authors believe that the animal models of traumatic osteoarthritis show different characteristics, depending on the animal species and modeling methods used. In other words, different modeling methods should be selected according to the use of different model animals. The reported methods in the post-traumatic osteoarthritis animal model can be found in Table 1.

As mentioned earlier, many papers have reported on molding animal models of osteoarthritis and developing spontaneous osteoarthritis animal models under natural conditions. The molding method is more mature and lacks deliberate human handling. The molding method can also lead to the use of a variety of animal species. Therefore, the aim of this paper was to summarize and analyze the methods of molding PTOA models by artificial induction, namely, intra-articular surgical methods, such as anterior cruciate ligament autologous in situ reconstruction (ACL-R) model.

Fig. 5. Anterior cruciate ligament autologous in situ reconstruction (ACL-R) model.

Fig. 6. Intra-articular fracture (IAF) model.
Animal models of traumatic osteoarthritis have different characteristics, depending on the animals and modeling methods used. There is no standard animal model for the PTOA modeling. The authors suggest selecting appropriate experimental animals and modeling methods based on consideration of the project funds, experimental objectives and technical conditions to obtain the appropriate PTOA model and expected experimental results to provide guidance for clinical therapy.

Conflicts of interest

All contributing authors declare no conflicts of interest.

References


