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Review Article

# Post-Traumatic Arthritis of the Knee in an Animal Model Following ACL Reconstruction

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Submitted: 20 March 2018

Accepted: 21 April 2018

Published: 23 April 2018

ISSN: 2475-9112



Keywords
• ACL tear
• ACL reconstruction
• Post traumatic knee arthritis
• Animal models, Prevention of osteoarthritis

**Abstract**

Injury to the ACL poses the risk of post-traumatic knee arthritis. Osteophytes have been observed after experimental cross-section of ACL by several researchers and have been attributed to joint instability. Same studies demonstrated that ACL reconstruction may be associated with a higher prevalence of knee post traumatic arthritis. The present paper investigates if the implication that surgical procedure itself is among the predisposing factors for the initiation of OA of the knee in animal models. 11 studies in animal models selected at random met the inclusion criteria and were assessed for the presence of post traumatic arthritis following ACL reconstruction or sham operation. The findings of the studied articles indicate that ACL sensory loss, blunt trauma to articular cartilage, immediate ACL reconstruction and/or bio-enhanced treatment may contribute to joint dysfunction and subsequent arthritic cartilage changes. The impact of surgical procedure for the development of post traumatic-like cartilage changes, has not yet effectively explored. Further investigation, especially designed, is needed for the detection of the implication of surgical procedure for post-traumatic arthritic changes.

## ABBREVIATIONS

ACL: Anterior Cruciate Ligament; OA: Osteoarthritis; PCR: Polymerase Chain Reaction; Collagen I: Type I Collagen Protein; Collagen III: Type III Collagen Protein; Alpha-SMA: α-Smooth Muscle Actin; MMP-1: Matrix Metalloproteinase-1; MMP-13 Expressions: Matrix Metalloproteinase-13 Expressions; ECM-Platelet Composites: Extracellular Matrix Platelets Composites; mRNA: Messenger RNA, qPCR: Quantitative Polymerase Chain Reaction; MLRA: Multiple Linear Regression Analysis

## INTRODUCTION

Injury to the ACL poses the risk of post-traumatic knee arthritis. The role of instability as a predisposing factor for cartilage degeneration was highlighted early. Knee post-traumatic arthritis remains a tremendous public health concern, both in terms of health-related quality of life and financial burden of disease [1]. Osteophytes have been observed after experimental cross-section of ACL by several researchers since 1969 and have been attributed to joint instability [2-7]. Alice et al. [8], emphasize that "Articular cartilage is devoid of blood vessels, lymphatics, and nerves and is subject to a harsh biomechanical environment. Most important, articular cartilage has a limited capacity for intrinsic healing and repair".

Bone bruises represent a blunt injury to the articular cartilage, subchondral bone, bone trabeculae and marrow. This relatively high occurrence in acute ACL injuries might play a role for the initiation of OA [9]. La Prade et al. [10], investigated in dogs the effects of notchplasty and sham intervention in the area. They found that areas of notchplasty showed statistically significant filling-in with lamellar bone and fibro cartilage. The goal of surgical treatment is to stabilize the knee, to reduce future meniscal lesions, and to delay post-traumatic arthritis. ACL reconstruction is considered as the treatment of choice for symptomatic ACL-deficient patients and can assist in full functional recovery. Some studies demonstrated that ACL reconstruction may be associated with a higher prevalence of knee OA. In a recent prospective cohort study was shown that radiographic evidence of post-traumatic arthritis is present 10-15 years following ACL reconstruction. What was not so far investigated is the possible role of surgical procedure in the initiation of knee OA [11].

## THE IMPLICATION OF SHAM OPERATION AND THE ROLE OF ACL SURGICAL RECONSTRUCTION IN THE INITIATION OF OSTEOARTHRITIC CHANGES IN EXPERIMENTAL ANIMAL MODELS

A total of 11 studies selected at random from the Web met the inclusion criteria and were assessed for the presence of post traumatic arthritis in animal models treated with anterior cruciate ligament reconstruction. The inclusion criteria were experimental cross-section of the ACL, immediate reconstruction, sham operation and correlation of surgery with the initiation of cartilage lesions.

Nagelli et al. [12], hypothesized that ACL sensory denervation would manifest in knee joint dysfunction and development of early post traumatic arthritis. Nine adult research dogs underwent arthroscopic surgery were divided in three treatment groups: partial ACL tear, ACL denervated and whole-joint denervated with a neurotoxin injection directly into the ACL or into the joint space, while a sham procedures were done on contralateral knees. The results of their study indicate that ACL sensory loss may contribute to joint dysfunction and subsequent OA changes.

O'Brien et al. [13], have tested, in five sheep, the hypothesis that immediate reattachment of anterior cruciate ligament can prevent kinematic changes and the development of osteoarthritis. Animals from a previous study served as sham or non-operated controls. In this study the combined differential morphology scores of the sham (2.9) and non-operated joints (0.8) were not significant, despite reasonably large animal numbers in each group (7 and 17, respectively). Their study indicates that 20 weeks following nearly anatomic ACL reconstruction, morphological changes consistent with the development of mild post traumatic arthritis do develop.

Fleming BC et al. [14], randomized fifty-five adolescent mini-pigs to 5 treatment groups and among them; untreated ACL transection, conventional ACL reconstruction, and bio-enhanced ACL reconstruction using platelet-rich plasma. The graft biomechanical properties, anteroposterior knee laxity, graft histology and macroscopic cartilage integrity were measured. The extent of cartilage damage in knees treated with the ECM-platelet composites was at 15 weeks significantly less than that of traditional ACL reconstruction.

Bozynski et al. [15], studied the effects of partial transection versus synovial debridement of the ACL in 27 dogs that were randomized in three ACL groups: sham control, intact ACL with synovial debridement, and partial transection of the ACL. They noted that more severe joint pathology and radiographic scores for post traumatic arthritis were present in the partial tear ACL group compared with exposed and/or sham control group.

Murray and Fleming [16], found in 64 mini-pigs that following bio-enhanced ACL repair, in which a bioactive scaffold was used to stimulate healing of an ACL transection, that the healing on the articular cartilage is affected. The biomechanical properties of the ligament or graft were examined and macroscopic assessments of the cartilage surfaces were performed after 6 and 12 months post-surgery. The macroscopic cartilage damaged area was significantly less than that in untreated ACL, the transected and bio-enhanced ACL reconstruction, and that there was a strong trend for less macroscopic cartilage damage than in conventional ACL reconstruction in the porcine model at 12 months.

Xie X et al. [17], 2013, investigated how platelet-rich plasma enhances autograft revascularization and re-innervation in a dog model of anterior cruciate ligament reconstruction. In the sham group, only the knee joints were exposed. In the normal control group, no surgery was performed on the knees. The real-time polymerase chain reaction examination using primers was significantly increased in the sham group compared with those in the normal control group at 2 week after surgery. They observed a time-dependent change in gene expression after ACL reconstruction surgery.

Papachristou G et al. [18], used 18 white New Zealand rabbits, for reconstruction of anterior cruciate ligament using the doubled tendon technique with the median one-third of the patella tendon replacing the anteromedial bundle and semitendinosus tendon replacing the posterolateral bundle of the ACL. Thus partly was reproduced the anatomical configuration of the ACL. The animals were divided into four groups and were scarified at 3, 6, 12 and 22 weeks after surgery. Femur-ligament-tibia complexes were evaluated at 3, 6, 12 and 22 weeks postoperatively for gross morphology and histological appearance. In the joints of rabbits that were scarified at 12 and 24 weeks were detected osteoarthritic lesions.

Heard BJ et al. [19], measured synovial biomarkers to determine if the mRNA expression of inflammatory and degradative molecules in the synovium correlate to changes in joint tissues in eighteen skeletally mature female sheep. Six models were served as non-operated control group. Synovium was harvested and mRNA expression quantified using qPCR. Multiple linear regression analysis (MLRA) was utilized to correlate synovial mRNA expression in treated and contra-lateral limbs, from all treatment groups with corresponding joint scores. Synovial mRNA expression was significantly elevated in all experimental and sham joints. Osteophytes were only present in surgical and sham animals. Findings suggest that this set of synovial biomarkers is predictive of early gross changes of joint tissues and particularly to early osteophyte formation, in vivo.

Heard BJ et al. [20], have investigated if inflammation following a defined knee surgery with the administration of a single glucocorticoid dose could prevent the development of post-operative-like OA changes.48 rabbits were randomly allocated into one of seven groups and among them: control group, sham (arthrotomy) and drill injury. At 48 h post-surgery investigation, dexamethasone treatment significantly lowered the mRNA levels for a subset of pro-inflammatory mediators, and significantly lowered the histological grade. Nine weeks post-surgery investigation, dexamethasone treatment significantly lowered the histological scores for synovium, lateral femoral condyle, and lateral tibial cartilage samples. The single administration of dexamethasone resulted in the preservation of proteoglycan content within the cartilage, as compared to cartilage from untreated joints, and that in turn may maintain the structural composition of the tissue making it less susceptible to structural damage.

According to Kiapour et al. [21], in sixteen mini-pigs that underwent unilateral ACL transection and were randomly treated with ACL reconstruction or bridge-enhanced ACL repair to test the hypothesis if the structural and anatomic properties of the reconstructed graft or repaired ACL correlate with the total cartilage lesion area 1 year after ACL surgery. The tensile properties, cross-sectional area, and multiplanar alignment of the healing ACLs or grafts and AP knee laxity in reconstructed knees were associated with the extent of tibiofemoral cartilage damage after ACL surgery. The results of their study support the hypothesis that multiple biomechanical and anatomic properties of the reconstructed graft or repaired ACL are related to the damaged cartilage lesion area following ACL surgery.

Attia E et al. [22], did in thirty-six New Zealand white rabbits partial or complete cross section of the ACL, while the contralateral ACLs were either sham operated or completely transected. Ligament tissue was harvested at 1, 2, or 6 weeks after surgery, and real-time PCR was performed using primers for collagen I, collagen III, alpha-SMA, MMP-1, and MMP-13.They measured after surgery, a real-time PCR using primers for collagen I, and III, alpha-SMA, MMP-1, and MMP-13 expressions that were found increased. These data that emerged provide support for the hypothesis that there is a time-dependent alteration of anabolic and catabolic matrix gene expression after injury/loss of ligament integrity. They considered that the resulting findings could contribute to the development of osteoarthritis.

## DISCUSSION AND CONCLUSION

Many investigators have observed the presence of post traumatic arthritis, both in humans and in animal models [2-7,23]. The initiating factors are not yet fully understood. Some investigators [5,22], noted a very early initiation of post traumatic arthritis. This observation raises the question of the possible role of surgical procedure itself for the early presence of post traumatic arthritis.

Immobilization [24], in experimental models, for whatever reason, is one of the pathogenetic factors in musculo-skeletal degeneration, as was supported by Videman [25].

Marks et al. [22], suggested that compression injury to the cartilage that exceeds a physiological threshold, inevitably leads to cartilage degeneration. In animal studies, the development of experimental post traumatic arthritis begins on the 3rd day[5] and continued throughout the experiment. Christiansen et al. [26], although they observed a rapid loss of trabecular bone by 7 days post-injury, noted that deterioration of articular cartilage was evident by 56 days post-injury, consistent with development of mild post traumatic arthritic changes.

Degeneration of articular cartilage both in humans [2,3,23] and in animal models [4-7], was seen in ACL deficient knees.

Sensory loss or denervation of ACL was hypothesized by Nagelliet al. [12], in experimental dog models that would lead in knee joint dysfunction and development of early post traumatic arthritis. The results of their study indicate that ACL sensory loss may contribute to joint dysfunction and subsequent arthritic cartilage changes.

The consequences of notchplasty were studied by La Prade et al. [10], in dogs. They have stated that "without a detectable instability of the joint, the notchplasty areas showed a time dependent filling-in with lamellar bone and fibrocartilage that was statistically significant at both 3 and 6 months".

The effects of partial transection versus synovial debridement of ACL were studied by Bozynski et al. [15], in dogs. More severe ACL and whole-joint pathology, as well as radiographic scores for osteoarthritis were present in the partial tear ACL group compared to exposed and/or sham control group.

Animals that underwent a sham operation and the ACL remained intact did not develop OA lesions in the articular cartilage according to Devitt et al. [16], while Heard et al. [17], have stated that osteophytes were only present in surgical and sham animals. According to Attia E et al. [23], the resulting findings with increased real-time PCR values from their experiments, could contribute to the development of osteoarthritis [27,28].

The present paper investigates the possible role of surgical intervention in the development of post traumatic OA following ACL reconstruction. The current information on post traumatic arthritis comes from both clinical and preclinical studies. According to Kuyinu et al. [29], "while there are known similarities in the disease process between animals and human's just one animal model, is not sufficient to study all features of osteoarthritis. The translatability of the results of each model to the human clinical condition varies". Teeple E et al. [30], stated that "The purpose of animal models of osteoarthritis is to reproduce the pattern and progression of degenerative damage in a controlled fashion, so that opportunities to monitor and modulate symptoms and disease progression can be identified and new therapies developed".

Surgical management protects the involved subjects from joint malfunction and minimizes the possibilities to develop post traumatic arthritis. Nevertheless, no matter the surgical procedure, post traumatic arthritis is developed in a number of cases. The increased rate of post traumatic arthritis after the reconstruction of the ACL may have an explanation. Probably trauma, apart from the produced instability may cause no detectable damage to the articular cartilage which over time promotes the development of post traumatic arthritis.

In experimental studies, where the joints of the animals do not have any kind of trauma, it is likely that the surgery affects the development of post-traumatic arthritis. Fleming et al. [14], found that the extent of cartilage damage in knees treated with the ECM-platelet composites was less significantly than that of traditional ACL reconstruction. Murray and Fleming [16], noticed that there was a strong trend for less macroscopic cartilage damage following ACL transection and bio-enhanced ACL repair than in conventional ACL reconstruction in the porcine model at 12 months. Xie X et al. [17], checked the effects of autologous platelet-rich plasma as a potential promoter of tendon healing. Following surgery they performed real-time polymerase chain reaction using primers that were significantly increased in the sham group, compared with those in the normal control group. They observed a time-dependent change in gene expression after ACL reconstructed surgery. Although, the involved cartilage there is less extended following the bio-enhancement treatment, still the development of post traumatic arthritis does exist. Papachristou et al. [18], investigated ACL reconstruction in white rabbits and found both macroscopically and histologically osteoarthritic lesions. They concluded that they do not know whether these lesions were due to arthrotomy, to drilling during the procedure or to the absence of the ACL. O'Brien et al. [13], concluded that "our study indicates that following nearly anatomic ACL reconstruction, morphological changes consistent with the development of mild OA do develop".

That trauma influence the development of OA is well accepted by the medical community. The current literature provides some evidence that ACL reconstruction does slow the onset of OA in the knee both in preclinical and clinical studies. Recent papers

focused on the use of biodegradable matrices to achieve knee stability and permit tissue regeneration [31].

Surgery or local trauma caused by the surgeon should be implicated in the onset of post-traumatic arthritis. Paschos [27], in a meta-analysis of six studies evaluating progression of OA after ACL injury concluded that ACL reconstruction can prevent OA development to a certain degree. In certain occasions, ACL reconstruction may be associated with a higher prevalence of knee OA. In his photoelastic study, Papachristou [32], stated that "correction of the femoro-tibial axis leads to redistribution of isochromatics, isoclinics, stress trajectories, and contact stresses. The values of the above parameters were corrected and approached those of normal knee, but in no case correction attained normal rates.According to Kuyinu et al. [29], "regrettably, no gold standard exists in the literature for animal studies and translation from in vitro to in vivo studies, then clinical studies, has met with difficulties".

The relationship between abnormal joint loading and/or surgical procedure and the onset of OA remains unknown. The pathophysiology of post-traumatic arthritis has not been explained. The increased rate of post traumatic arthritis after the reconstruction of the ACL may have an explanation. Probably trauma, apart from the produced instability may cause no detectable damage to the articular cartilage which over time promotes the development of post traumatic arthritis. It seems that is not only the magnitude neither the type of injury that determines the future of an injured articular surface.

## LIMITATIONS OF THE STUDY

A. This is a small number of published papers with reference to early post traumatic changes in experimental animal models.

B. The above mentioned papers were not designed for the investigation of the implication of the surgical procedure in the initiation of post traumatic changes.

## CONCLUSIONS

ACL reconstruction potentially restores knee stability and appears to reduce the risk of post traumatic arthritis, but it cannot fully eliminate the increased risk of arthritis. The impact of surgical procedure for the development of post traumatic-like cartilage changes, has not yet effectively explored. Further investigation, especially designed, is needed for the detection of the implication of surgical procedure for post-traumatic arthritic changes.

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**Cite this article**

*Papachristou G (2018) Post-Traumatic Arthritis of the Knee in an Animal Model Following ACL Reconstruction. JSM Foot Ankle 3(1): 1048.*