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REVIEW ARTICLE

What have animals taught us about total joint arthroplasty ? A review of the literature

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Animal models for total joint arthroplasty (TJA) have been reported on extensively in the literature. This work seeks to objectively review the most relevant and recent studies performed using these models, and to provide insight into the strengths and weaknesses of each. The terms joint arthroplasty and animal model were searched on Pubmed on March 1, 2015. Animal models included bovine, canine, ovine, goat, rat, and rabbit. Much of the work in animal models for TJA has focused on the biologic response to novel materials, biologics, and surgical techniques ; as interest grows the use of animal models may increase.

Keywords : joint replacement ; arthroplasty ; animal model

INTRODUCTION

Total joint arthroplasty (TJA) is a common orthopaedic procedure during which a damaged, typically arthritic articular surface is excised and replaced with prosthetic components. Its origin is associated with amputations performed in the 1700s by English surgeons to treat industrial injuries *(17)*. It was not until the end of the 19th century that the first hip and knee replacements were performed in Germany by Dr. Themistocles Gluck, who conducted his preliminary research in animals before attempting joint replacements in humans *(15)*. However, the origin of modern joint replacement is typically credited to Dr. John Charnley, who first used acrylic cement in 1961 to perform a hip arthroplasty *(9)*. Today, hip and knee arthroplasty is considered one of the most successful surgical procedures in medical history for its ability to reliably relieve pain and restore function *(32)*. This success has been built upon a robust foundation of research, some of which has been performed in animal models *(3,28)*.

Orthopaedic diseases have been most widely studied in canines, partially because they co-habit the same living environments as humans and endure many of the same musculoskeletal stresses *(28)*. Furthermore, canines are one of the few species with a wide range of body morphology, which, as in humans, may predispose to certain pathologic musculoskeletal conditions *(28)*. Many other animal models have been employed, however, the most befitting model is dependent upon the specific research question *(39)*. For example, mice are

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relatively better characterized genetically than other species, which has resulted in their use as common model for basic science research. Canine and ovine species are generally larger animals, and may be more appropriate for studying biomechanics or surgical technique. Previous work has successfully reviewed and categorized these models for other diseases, such as osteomyelitis *(30)*.

There have been many studies of total joint arthroplasty in the literature that have used animals to test various hypotheses. There has been no literature summarizing these results, and no studies which have identified the ideal animal model for future work. The goal of this work was to perform a review of the existing literature regarding animal models for hip and knee arthroplasty, and to identify and categorize the strengths and weaknesses of each.

METHODS

The terms joint arthroplasty and animal model were searched on Pubmed on March 1, 2015. Animal included bovine, canine, ovine, goat, rat, and rabbit. These species were chosen for their prevalence in studies of orthopaedic surgery and use as models for musculoskeletal disease. The most robust and relevant studies were selected for inclusion in the review. The studies selected were categorized by animal, and sub-categorized as follows : 1) effects of bisphosphonates, 2) testing of novel materials, 3) biological factors and their role in osseointegration, 4) native tissue response to arthroplasty, and 5) novel surgical techniques.

RESULTS

Canine

Canine models for TJA were among the earliest reported. They continue to be used extensively and remain the subject of wide publication.

Effects of Bisphosphonates

In 1991, Soballe et al. performed one of the early studies examining the effect of hydroxyapatite (HA) coating on titanium implants in the setting of osteopenia *(37)*. The authors induced an osteopenic arthritis in the right knees of twelve dogs, then inserted cylindrical implants into the bilateral lateral femoral condyles, with the unaffected knees serving as controls. Six dogs received bilateral titanium implants and the other 6 dogs received HA coated implants. They determined that while implants with titanium coating in osteopenic bone had significantly lower bone-implant shear strength, HA coating negated the effect of osteopenia. In contrast, titanium coating produced a stronger bone-implant interface than HA coating in non-osteopenic control bone. This was followed several years later by Maistrelli et al., who compared cementless hip hemiarthroplasty using titanium implants coated with HA against grit-blasted controls *(24)*. They reported significantly higher interface shear strength and increased bone apposition for HA treated implants. In 2000, Al Hertani et al. expanded on this concept further by studying the optimal extent of HA coating *(2)*. The authors reported increased micromotion in half-coated compared to completely coated stems at 3 weeks, but not at 3 or 12 months. Additionally, complete HA coating resulted in significantly more bone apposition, wider trabecular strut measurements, and more robust periprosthetic bone *(2)*.

Other researchers have focused on the effect of systemic bisphosphonate therapy on joint arthroplasty. In 2005, Wise et al. performed total hip arthroplasty (THA) in 30 dogs, and purposefully caused aseptic loosening by implanting polyethylene debris into cavities within the femoral stem *(44)*. The authors reported that zoledronate therapy significantly decreased bone turnover and significantly increased new subperiosteal bone formation *(44)*. High dose therapy increased strength and decreased porosity of cortical bone. Later, Soballe et al. simulated micromotion of the implant to evaluate the added effect of alendronate therapy in the setting of revision arthroplasty. They found that absolute stability of the implant in revision arthroplasty is superior to administration of alendronate therapy in unstable implants *(36)*.

Most recently, Sorensen et al. studied the effect of zoledronate-soaked allograft in revision arthroplasty *(38)*. In this case the authors found that bisphosphonate-soaked allograft resulted in significantly increased ultimate shear strength and stiffness, as well as significantly more allograft bone remaining at the surgical site after 4 weeks.

Testing of Novel Materials

A variety of questions regarding the use of optimal materials in arthroplasty have been addressed in canine models. In one early study, Harvey et al. investigated the effect of femoral stem stiffness on stress shielding and fixation in a canine cementless THA model *(19)*. This was accomplished by performing bilateral THA with both a stiff titanium stem and a flexible composite stem. The authors did not detect a significant difference in stress shielding or cortical area between the two groups ; they did, however, find a significant decrease in bone ingrowth for flexible stems. The authors interpreted this to mean that a balance must be acknowledged between preventing stress shielding and encouraging stability, and that excessively flexible stems do not improve the former and may negatively affect the latter *(19)*.

Other work has focused on fixation of the acetabular cup : Bobyn et al. investigated acetabular components made with a porous tantalum backing and found good bone ingrowth at all sections of the implant *(7)*. Yee et al. compared biodegradable, polyglycolide-lactide screws versus titanium screws for initial stabilization of the acetabular cup *(45)*. They reported that the biodegradable screws were significantly weaker when biomechanically loaded to failure at time-zero, but that bone ingrowth over time was not significantly different between the two groups *(45)*.

Biologic Factors and Their Role in Osseointegration

Canine models have also been used to study the effects of a number of exogenous compounds on osseointegration. In 1995, Cook et al. used a canine model to investigate the effects of indomethacin on bone-interface strength *(11)* The authors implanted multiple cylindrical titanium implants bi-cortically into canine femurs. They then applied various indomethacin dosing schemes to multiple groups of animals, and ultimately concluded that while indomethacin did negatively affect bony ingrowth initially, there was no difference beyond six months of treatment *(11)*.

Another area for research has been the use of growth factors to study osseointegration in arthroplasty. In 2003, Bragdon and colleagues studied the effect of bone morphogenetic protein-2 (BMP-2) on bone formation in a THA model *(8)*. The authors also investigated the effect of a calcium phosphate “carrier” in combination with BMP-2 treatment. Their results demonstrated improved defect coverage when both BMP-2 and the carrier were applied to the gap. Notably, they did not see improved implant ingrowth. More recently, Saran et al. analyzed the effect of Osteogenic protein-1, also known as bone morphogenetic protein-7 (BMP-7), on osseointegration following femoral replacement with a diaphyseal prosthesis *(34)*. They found increased bone ingrowth and bone apposition after treatment with BMP-7 compared to a control group *(34)*.

Native Tissue Response to Arthroplasty

Some of the earliest work performed in canine models focused on the response of bone and soft tissue to arthroplasty. In 1988, Sandborn and colleagues published a paper describing their work on the measurement of bone ingrowth for non-cemented arthroplasty *(33)*. The authors surgically implanted intramedullary implants which contained multiple regions of varying thickness into the femurs of six dogs in order to evaluate multiple implant-bone gap distances. They found that ingrowth was achieved with gaps as large as 2 millimeters (mm), but when the gap was greater than 0.5mm, the bone was histologically disorganized *(33)*. Other early noteworthy work was performed in 1991 by Page et al., which focused on bone strains and stress shielding following cementless arthroplasty *(29)*. The authors measured strain at multiple anatomic locations both in the intact state and following hip arthroplasty. The results showed consistent decreases in strain about the femur following arthroplasty, particularly proximally and medially *(29)*.

More recently, the literature has focused on a variety of topics related to tissue response. A 2005 study by Minihane et al. studied the effect of hemiarthroplasty on acetabular bone and cartilage *(25)*. The authors found degenerative changes of the cartilage in hips treated with hemiarthroplasty, as well as decreased subchondral bone volume, but not thickness *(25)*. In 2013, Syed and colleagues evaluated the effect of three different femoral preparation techniques (reaming only, cementing, and pressurized cementing) on cortical bone mineral density *(40)*. They found that reaming most significantly decreased bone density, and that cementing after reaming resulted in additional decreases in density. They suggested that femoral stems which reduce or eliminate the need for preparatory reaming may be advantageous in terms of maintaining bone density *(40)*.

Novel Surgical Techniques

A number of canine studies have focused on surgical techniques for arthroplasty. One such area of research has been a series of papers by Soballe and colleagues, in which they describe and evaluate a "crack revision" technique for revision arthroplasty *(4,14)*. In an early study of this nature, the authors implanted a micromotion device into canine femurs. The femurs were revised 8 weeks following the first intervention, and half were treated intraoperatively with a custom device that was capable of cracking the thin layer of sclerotic bone surrounding the implant. The other half received no special treatment beyond curetting and lavage. The result was significantly greater shear strength and shear stiffness for the crack revision group on biomechanical testing, as well as reduced fibrous tissue and better bone ongrowth at four weeks following revision *(14)*. As a follow up study, Baas et al. compared the crack revision technique to reaming *(4)*. They demonstrated a similar pattern with regard to mechanical strength, but found no difference in bone-implant ongrowth between cracking and reaming *(4)*.

Ovine

Novel Surgical Techniques

Although sheep have only recently gained attention in TJA research, they may represent a more relevant model to arthroplasty in humans *(31)*. One of the first arthroplasty studies conducted in sheep was performed by Phillips et al. in 1987 *(31)*. The authors performed unilateral hip resurfacing and found a 58% rate of femoral loosening after 10 months. This led the authors to suggest the use of sheep over canine models, since the relatively high loosening rate would be a more rigid test and more closely reflect arthroplasty in humans.

Biologic Factors and Their Role in Osseointegration

In 2008, Korda et al. studied a mesenchymal stem cell (MSC)-allograft mixture in the setting of hip hemiarthroplasty *(23)*. After a twelve week healing period, the authors measured the ground reaction force of the affected limb, and found no significant effect. Bone formation was also measured via histology, and demonstrated significantly more growth at the interface between the allograft and implant in animals treated with MSCs *(23)*. This work was followed by Dozza et al., who compared the effect of MSCs and platelet lysate on bone formation after hemi-arthroplasty *(13)*. Similarly, they demonstrated increased bone growth when MSCs were used.

Testing of Novel Materials

Müller-Rath et al. evaluated the effect of acetabular preparation with amphiphilic bonder prior to implantation of a cemented acetabular cup for the purpose of sparing subchondral bone *(26)*. After nine months the authors reported no obvious loosening in the bonder group, but a 70% loosening rate among control specimens. Additionally, on microscopic examination they found a fibrous layer at the bone-cement interface in the control group, but not in the bonder group. They suggested that the use of amphiphilic bonder may improve fixation in a situation where the surgeon wishes to spare as much acetabular subchondral bone as possible *(26)*. A later study by Timperley et al. evaluated the effect of hydroxyapatite paste at the cement-bone interface of the acetabular cup *(41)*. Use of this paste decreased the number of radiolucencies observed on imaging. Additionally, there were more animals with an osseointegrated interface in the hydroxyapatite group. Finally, a recent paper by Nakahara et al. described the use of carbon fiber-reinforced polyetheretherketone (PEEK) in arthroplasty *(27)*. They demonstrated stability in all implanted femoral stems, and in 40% of cementless acetabular components. None of the cemented acetabular cups were stable, most often due to failure at the cement-bone interface *(27)*.

Bovine

Novel Surgical Techniques

Bovine models for joint arthroplasty have not been reported on extensively in the literature, but a handful of in vitro studies have been published. In 2009, Ackland et al. used bovine femurs to compare four methods for cleaning the femoral canal *(1)*. The authors tested standard normal saline irrigation, pulse lavage, packing of the femoral canal with hydrogen peroxide-soaked gauze, and a pulse lavage-hydrogen peroxide gauze combination technique. They demonstrated significantly greater force was required to cause failure in specimens that had been treated with pulse lavage. More recently, Baker et al. used bovine femoral heads to study the effect of peripheral reaming on bone temperature *(5)*. The authors found that irrigation during reaming significantly decreased external bone temperature when compared to dry reaming, and that irrigation with 0.8° C water reduced temperature below the threshold for osteocyte death. However, internal bone temperature did not change significantly regardless of the use of irrigation *(5)*

Goat

Novel Surgical Techniques

The earliest report by Khalily et al. described a safe and effective operative approach to the goat hip *(22)*. Similar to the posterior approach to the hip, the authors suggest an incision over the cephalad one-third of the greater trochanter extending 1cm dorsally and inferiorly to one-third of the way down the femoral shaft. Following adequate dissection of the gluteal muscles and short external rotators, the surgeon can achieve subluxation of the femoral head by internal rotation and flexion. Similarly, internal rotation and adduction of the limb exposes the femoral shaft. Postoperatively, the authors suggest continuous intravenous first generation cephalosporin for 24 hours. A full body sling is recommended for the first 72 hours, to prevent dislocation. Periprosthetic fracture is known to be difficult to treat in the goat as the femoral cortex is thin *(22)*.

Native Tissue Response to Arthroplasty

One early study by De Waal Malefitj et al. described vascular changes following uncemented and cemented arthroplasty *(12)*. In 13 goats, the micro and macro vascular responses were examined pre and posthumously. On microvascular examination, there were similar metaphyseal and diaphyseal patterns of vascularization at week 1 in both cemented and uncemented cohorts. The uncemented cohort had more radially oriented vessels through the cortex that extended into the endosteal portion of the cortex by week 3, which was not seen in the cemented group until week 5 *(12)*. Kalia et al. used the goat hip to study the effect of autologous-bone marrow derived stem cells in prevention of aseptic loosening *(21)*. The authors mixed these cells into the fibrin glue used on the surface of hydroxyapatite-coated uncemented acetabular components while the control group received fibrin glue only. Overall new bone growth adjacent to the bone implant interface increased in the treatment group, but was not statistically different *(21)*. New bone growth found at the periphery of the cup compared to the control was significantly different. Similarly, bone-impact contact was significantly greater and fibrous tissue membrane was significantly reduced in the treatment groups *(21)*.

Biologic Factors and Their Role in Osseointegration

In 1998, Vercaigne et al. studied the effects of titanium plasma-sprayed particles to enhance biological performance *(42)*. Their hypothesis was based on several studies that showed rough microsurfaces performed better than smooth implant surfaces. Implants were sprayed with Titanium-2, Titanium-3, and Titanium-4 particles. Histological analysis showed no significant difference in bone contact or bone mass *(42)*. Walschot et al. used the goat hip to study impaction grafting and osteoconduction *(43)*. Specifically, the authors were interested in the effects of uncoated and porous titanium particles (TiP) versus porous biphasic calcium-phosphate (CeP) and allograft bone particles (BoP) on bone ingrowth distance. Measured via fluoro-chrome labeling and histology, the authors found that bone ingrowth was significantly improved for TiP compared to BoP and CeP. In contrast, cross-sectional bone area was smaller in CeP and TiP compared to BoP *(43)*.

Rat

Biologic Factors and Their Role in Osseointegration

Hayashi et al. utilized an ovariectomized rat model to evaluate the osteogenic effects of prostaglandin EP4 agonists on hydoxyapatite implants compared to saline treatment *(20)*. They found that the EP4 agonist improved the osteoporosis, ultrastructure, and mechanical properties of the implant. In a 2010 study, Choi et al. evaluated the novel approach of using a sleeve between the implant and the bone in a cementless fixation *(10)*. The authors compared traditional cemented fixation against the sleeved implant by measuring bone volume and interface strength in a rat model and found no difference between approaches.

Functionalized surfaces have been shown to reduce osteoporotic bone loss, reduce implant-related infection, and aid in osseointegration *(46)*. In 2013, Zankovych et al. sought to evaluate the effect of polyelectrolyte multilayer coatings on osteoblast proliferation compared to native titanium alloy *(46)*. They used a rat tibia model to evaluate chitosan/gelatine or chitosan/hyaluronic acid coatings with either a terminating layer of gelatine or hyaluronic acid. There was a significant increase in shear strength in both the chitosan/gelatine and chitosan/hyaluronic acid groups compared to control, but no difference in bone contact or bone area between groups *(46)*.

Native Tissue Response to Arthroplasty

Polyethylene wear has been linked to osteolysis and decreased joint lifespan in TJA, therefore, Smith et al. examined the macrophage response to polycarbonate-urethane (PCU) as an alternative to polyethylene acetabular components *(35)*. Using a Ti-alloy femoral intramedullary nail rat model, the authors compared endotoxin free cross-linked ultra-high molecular weight polyethylene (x-UHMWPE) versus PCU particles. On microCT and mechanical testing, the x-UHMWPE group was found to have less bone mass and decreased fixation strength than the PCU group, suggesting that the PCU particles may be less disruptive to the bone-implant fixation process *(35)*.

Rabbit

Biologic Factors and Their Role in Osseointegration

Aluminum prostheses have been used in THA, however the aluminum/bone interface may be less robust than desired ; this was addressed by Hamadouche et al *(18)*. The authors sought to evaluate the osteoconductive properties of aluminum implants coated with sol-gel bioactive glass in a rabbit model. In comparison to aluminum-only implants, the authors found a greater percentage of bone in direct contact with the sol-gel bioactive glass coated implants.

The small peptide ligand arginine, glycine, and aspartic acid (RGD) has been shown to increase the adhesiveness of implant surfaces for osteoblasts, a property that inspired Bitschnau et al. to evaluate the addition of RGD to hydroxyapatite (HA) in comparison to pure HA and uncoated stainless Kirschner wires *(6)*. They evaluated new bone formation, implant bone coating, and biocompatibility in a rabbit tibia model. There was no significant differences in new bone formation, implant bone coating, or number of multinucleated giant cells at the 4 & 12 week marks.

Native Tissue Response to Arthroplasty

Fornasier et al. (2004) sought to determine the difference in tissue response to polyethylene and/or titanium particles *(16)*. They utilized a rabbit model of tibial implant failure to investigate the impact that each of these reactions had on peri-prosthetic osteolysis. They found that a mixture that contained both polyethylene and titanium particles caused the greatest amount of bone resorption. Furthermore, their study also showed that the degree of implant misalignment in their failure model was directly related to the amount of bone resorption *(16)*.

CONCLUSION

Much of the work on animal models for arthroplasty has focused on the biologic response to novel materials and components, although some authors have studied novel surgical techniques. Historically, canine models have been used extensively. Initial work in dogs focused on the effects of hydroxyapatite coated implants *(2,24,36, 37,38,44)*. Ironically, ovine models, first proposed to be advantageous over canine in the 1980s, have only recently become popular *(31)*. Much of the work in this model has focused on stem cell treated allografts and novel materials, such as carbon fiber implants *(13,23,27)*. Goat models have been useful for developing surgical technique, but experimentation with biologics and enhanced microsurfaces has not been performed extensively *(21,22,42,43)*. Rats have been used in studies attempting to improve osseointegration, and to demonstrate that other materials may be better tolerated than traditional polyethylene *(20,35)*. Investigators working with the rabbit model have provided direction for future efforts to improve implant fixation through specialized coatings, novel materials, and manipulation of the physical properties of implant materials *(6,16, 18)*.

In conclusion, there are a number of established animal models for total joint arthroplasty, each with their own strengths and weaknesses. As interest in the use of stem cells, biologics, and novel materials in orthopaedics grows, the use of animal models may increase.

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