Animal models relevant to cementless joint replacement

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Abstract

This review focuses on animal models used to study certain aspects of "cementless" joint replacement. Implants used in this application are designed to become attached to the host skeleton through either bone ingrowth into porous surfaces or bone apposition (ongrowth) onto other types of surfaces. Biological fixation of cementless joint replacement implants relies on intramembranous bone regeneration. We describe a framework for understanding research design in light of the type of research questions now being asked. In particular, species choice, implant design and placement, and experimental endpoints are described in some detail. We provide a summary of recent studies specifically focused on implant fixation, demonstrating that most work is still at the morphological and biomechanical levels with little understanding at the molecular level. We also provide a more comprehensive listing of studies using hip and knee replacement models, demonstrating that most work is focused on the interface, and responses of the immediately adjacent trabecular bone and the more distant cortical bone. We conclude by encouraging investigators to design their experiments so that there is enough power to answer a limited number of questions as opposed to providing limited data on a broader number of issues.

Keywords: Animal Models, Total Hip Replacement, Total Knee Replacement, Bone Regeneration, Implants

Introduction

Joint replacement is now considered one of the most successful surgical procedures because of reliable pain relief and return to function1. Currently, in the U.S. alone a conservative estimate is that more than 400,000 total hip and knee replacements are performed annually. In addition, a significant number of shoulder and small joint replacements provide pain relief and improved function in the upper extremity and foot. A smaller number of ankle replacements are performed each year. The basis of this success is a considerable research effort, including a large body of work relying on animal models2.

Here, we focus on certain aspects of “cementless” joint replacement. These implants are designed to become attached to the host skeleton through either bone ingrowth into porous surfaces or bone apposition (ongrowth) onto other types of surfaces. Sometimes, these processes are called biological fixation or osseointegration. The term osseointegration has been borrowed from dentistry3, where initially the term referred specifically to apposition of bone to titanium implants at the light microscopic level and implied the use of screw-shaped, commercially pure titanium devices placed with minimal trauma to the host bone in a two-stage surgical procedure. Use of the term osseointegration has now taken on a more general meaning to include fixation of implants by bone ingrowth or apposition in the absence of acrylic bone cement or a fibrous tissue interface.

The implants used today are designed to provide pain relief and improved function indefinitely, but there is increasing interest in providing biological reconstruction for injured or damaged joints4. This is already being accomplished with some success today through the use of osteochondral allografts and cartilage cell transplantation for relatively small lesions. However, for the extensive damage present in end-stage osteoarthritis, the most common indication for replacement of the hip or knee and certain other conditions including rheumatoid arthritis and osteonecrosis of the major weight-bearing joints, joint replacement with mechanical devices remains the most important option.

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In addition to the work on joint replacement, there has been extensive use of animal models in orthopedics to investigate the use of implants for other indications, especially fracture repair and spinal fusion. In these two indications and others, including even joint replacement, the definition of an implant is changing from a purely mechanical device (e.g., the femoral component of a hip replacement or a fracture fixation plate) to a biological device (e.g., a bone graft substitute used in conjunction with joint replacement or spinal fusion). While the mechanical devices are meant in many cases to endure the patient’s lifetime, the biological replacements are now being designed to be resorbed and replaced by functioning host tissue.

Here, we describe animal models used to study some aspects of cementless joint replacement, specifically implant fixation and the response of the host tissue to the presence of the implant, especially the functional adaptation of the adjacent trabecular and cortical bone. We have not attempted to include thorough discussions of animal models used to address other topics relevant to joint replacement such as particulate debris and prosthetic infection.

**Cementless fixation**

Biological fixation of cementless joint replacement implants relies on intramembranous bone regeneration, whether the tissue level mechanism is through bone ingrowth into a porous structure or bone ongrowth onto the surface of the implant. This type of fixation occurs if the implant (i) is made from a biocompatible material, (ii) has the appropriate surface characteristics, (iii) is mechanically stable, (iv) is in close initial contact with the host bone and (v) the implantation site is not infected. In addition to these customarily recognized requirements for bone ingrowth/ongrowth in orthopedics, in dentistry the need to minimize trauma to the host bone is considered a key surgical variable. Apparently, the use of porous coatings and other surface modifications in orthopedic implants has lessened the need to minimize trauma to the host skeleton at the time of surgery as well as the need to avoid immediate load-bearing. Enough information now exists from clinical studies and retrieved implants to indicate that cementless fixation with orthopedic implants does occur through bone ingrowth/ongrowth, with clinical results now often comparable to those achieved with the use of bone cement.

With both bone ingrowth and bone ongrowth/apposition, the long-term fixation is dependent upon a biological response from the host, specifically bone formation through the intramembranous pathway. Indeed, the early work with osseointegration was based on studies of intramembranous bone regeneration. The host skeleton forms woven bone as a normal response to the surgically induced damage created to prepare the anatomical site for the implant. An implant placed in this environment can then become fixed to the host if the conditions described above are present.

**Research questions and research design**

Research questions addressed with animal models include the appropriate implant surface characteristics (e.g., porous coating microarchitecture, surface chemistry and surface roughness), the effects of interface motion and gaps, the effects of adjuvant therapies used during joint reconstruction, and the role of bone grafts, bone graft substitutes and growth factors in enhancing implant fixation. In addition, there has been considerable interest in the functional adaptation of the host skeleton to the altered mechanical environment engendered by the presence of the implant. A number of reviews in the literature describing
many of these studies are currently available. In this section, we provide a brief review of methodological issues, including species choice, implant design and placement, and experimental endpoints. Additional methodological issues that we describe in some detail elsewhere include use of the contralateral bone as a control, sample size, and the time points to be examined.

Species choice

The most common species in use today include the dog and the rabbit. Less commonly used species include the goat, sheep, rat, mouse, pig and horse. Occasionally, primate models are used. Choice of the appropriate species is highly dependent upon the nature of the research question. For instance, if one were interested in gene expression at the interface, then a mouse or rat model would be helpful because of the availability of probes for these species. On the other hand, these species have not been used to study other issues, such as fixation in the presence of implant weight-bearing, where larger species are used.

Implant design and placement

In vivo models relevant to the function of joint replacement implants may be categorized as either non-weight-bearing or weight bearing. By definition, the non-weight-bearing devices are not directly loaded, are usually implanted for short periods of study (days to weeks) and are used to investigate implant material or the bone-implant interface isolated from the effects of cyclic weight-bearing. Most often, these models have been used to examine materials, coatings or surface modifications or the effects of treatments that may inhibit or enhance bone ingrowth. If a material or surface structure appears promising in a non-weight-bearing application, the next consideration is to test the concept under the influence of cyclic weight-bearing, usually a segmental replacement or joint replacement model (see below).

Non-weight-bearing implants can be implanted so that there is a press-fit with the host bone (i.e., initial intimate apposition between the implant surface and bone) or with an initial interfacial gap or defect (Fig. 1). The latter method is a simple means to create a model of inhibited implant fixation in which the ability of various surface treatments or materials to restore normal fixation can be tested. These implants can be placed with the long axis of the implant and bone aligned ("axial" placement) or with these two axes orthogonal ("transcortical" placement) (Fig. 2). The axial devices may be inserted into only the distal or proximal metaphyseal bone or through all regions of the bone, metaphyseal and diaphyseal. Transcortical devices can be placed in diaphyseal or metaphyseal regions, as well. Thus, the device geometry may allow apposition to only metaphyseal trabecular bone and the endosteal cortical surface of the diaphysis. Our belief is that axial and transcortical metaphyseal implants provide more clinically relevant information than transcortical diaphyseal implants because most joint replacement implants are placed within a trabecular bone bed (e.g., the acetabular component in total hip replacement and the tibial and femoral components in total knee replacement) or within the medullary cavity (e.g., the femoral components in total hip replacement).

A number of authors are now using bone chamber models. These models have certain advantages including the ability to perform vital microscopy and to make repeated tissue harvests over time. They have not been used as far as we are aware to study bulk implants, but the studies do contribute to understanding mechanisms of bone regeneration.

Recently, controlled motion models have been developed so that a major limitation of non-weight-bearing implants, lack of replication of load distribution from a weight-bearing prosthetic device to the bone, can be addressed. These models also make it possible to test specific hypotheses about interface motion and biological fixation.

Another model system that bridges some of the differences between non-weight-bearing and joint replacement models is the use of devices that communicate with the joint. For instance, this type of model has been used to investigate the role of particulate debris on cementless interfaces without the compounding effects of weight bearing and component movement. Controlled motion can also be imparted to this type of model.

Segmental replacement models, first developed in response to the need to replace large regions of long bone diaphyses severely injured by trauma are weight-bearing devices relevant to total joint replacement. These models have been developed in the dog and other species such as primates, goats or sheep.

A more common weight-bearing model, particularly in recent years, has been hip replacement (Fig. 3). This has been applied in two forms. One is a total hip replacement with both acetabular and femoral components being inserted. The other is a hip replacement hemiarthroplasty in which only the femoral head is replaced, thereby avoiding the potential complications of an acetabular component. The use of any joint replacement device in an animal model allows that device to experience the cyclic loading of ambulation both for the prosthetic device materials as well as the bone-implant interface. Although different surgical approaches have been utilized for the implantation of hip replacement components, this is a reliable model which can provide a very successful clinical function provided proper implantation of the device is achieved.

Variations on the bone-implant interface have also been studied by allowing the presence of only a press-fit or, alternatively, the development of defects in the bone adjacent to the implant. Thus, hip arthroplasties may be implanted as a press-fit device with the components being impacted into an undersized prepared cavity or as a gap model in which control defects are developed or created adjacent to the prosthetic bone interface. These defect models have been used to test various bone grafts and bone graft substitutes.

A further modification of the weight-bearing prosthetic joint model is the development of revision models that replicate the bony environment developed in the site surrounding a failed prosthetic device. The altered bony environment includes the presence of macrophage-laden granulomas rather than bone marrow at the site of implantation\textsuperscript{36}. Use of the primary and revision hip replacement models is detailed below.

Total knee replacement models have been reported, but much less frequently than total hip replacement models (Fig. 3). Most of these studies have focused on the bone-implant interface and are described in more detail below.

Experimental endpoints

Most studies rely on morphological or mechanical endpoints. An example of a morphological endpoint is the volume fraction of bone ingrowth into a porous coating\textsuperscript{37}. For implants lacking a porous coating, the researchers usually develop an index of bone apposition. Other morphological

<table>
<thead>
<tr>
<th>Question</th>
<th>ENDPOINT</th>
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<tbody>
<tr>
<td>Molecular/Gene Expression</td>
<td>Morphology</td>
</tr>
<tr>
<td>surface design (porous coating type, surface roughness, surface composition)</td>
<td>(71-91)</td>
</tr>
<tr>
<td>growth factors, bone grafts, bone graft substitutes</td>
<td>(95-97)</td>
</tr>
<tr>
<td>host factors</td>
<td>(83,127-130)</td>
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Table 1. Selected studies involving non-weight-bearing models published since 1998.
The choice of model depends upon the question being asked. For instance, if one is interested in testing whether a new surface design will support bone ingrowth/apposition or fixation, the simplest approach is to use a non-weight-bearing, press-fit model. In contrast, if one is questioning whether or not a new surface design, growth factor or bone graft substitute will enhance implant fixation, then the most efficient course of action would be to use models in which fixation is inhibited, perhaps progressing from simple to complex models (e.g., a non-weight-bearing gap model to a revision total hip replacement model).

Table 1 provides a sampling of studies using in vivo models reported since 1998 that examine issues related to implant fixation. The survey is certainly not exhaustive, but is representative of the type of work now being performed. Most of the studies derive their motivation from orthopedics, but some are craniofacial in nature. The studies in this table used non-weight-bearing models. Studies involving total joint replacement models are described later in this review. We have organized the studies according to the type of question being asked and the type of endpoint used in the experiment. It is obvious from Table 1 that there is considerable interest in the design of the implant surface and the use of growth factors, bone grafts and bone graft substitutes to enhance fixation. The former mechanical test is often used in non-weight-bearing models, while the latter is used in joint replacement models.

### Summary

The choice of model depends upon the question being asked. For instance, if one is interested in testing whether a new surface design will support bone ingrowth/apposition or fixation, the simplest approach is to use a non-weight-bearing, press-fit model. In contrast, if one is questioning whether or not a new surface design, growth factor or bone graft substitute will enhance implant fixation, then the most efficient course of action would be to use models in which fixation is inhibited, perhaps progressing from simple to complex models (e.g., a non-weight-bearing gap model to a revision total hip replacement model).

### Listing of non-weight-bearing animal models used to examine fixation only

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### Listing of studies using hip replacement models

Table 2 summarizes how total hip replacement models have been used. This table provides a comprehensive summary and is not restricted to the last two years because the total number of reports using these types of models is not nearly as great as the number for the non-weight-bearing models.

With the hip replacement models, most of the attention has been on morphological and biomechanical responses with an emphasis on one or more of three primary regions: (i) the interface, (ii) the adjacent tissue (usually medullary contents or trabecular bone) or (iii) the host cortical bone. While this classification scheme works for most studies, in some the focus has been elsewhere, such as the articular cartilage after hemiarthroplasty, cement restrictors, and embolism. A few studies have focused on biomaterial performance with little or no attention paid to the biological response.

### Models of knee replacement

Knee models are much less common and it is not necessary to summarize the studies in tabular format. One of the early studies used a knee model to characterize the mechanical properties of fibrous tissue at the bone cement-bone interface. Later studies used these models to investigate various interface phenomena, including the potential to establish bone ingrowth fixation.

More recently, knee models have been used to investigate the role of implant design on osseointegration or mechanical stability, bone grafting, wear of articular cartilage, embolism, hemorrhage control, wear debris, and infection.
Conclusion

It should be clear that there is no single model to be recommended because model choice depends upon the research question. In general, our view is that in designing an experiment it is more important to answer a limited number of questions than to have some information about many questions with no definitive answer. Practically, this usually means limiting the number of time points studied or the number of materials investigated so that adequate sample sizes can be used.

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