Review

Biocompatibility of total joint replacements: A review

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Abstract: Total joint replacement is one of the most clinically successful, cost-effective surgical procedures. These operations have been shown to improve pain, function and mobility in patients with end-stage arthritis. However, joint replacements that will allow full, unrestricted, high impact activities and last the patient's lifetime have not yet been devised. This is due to biocompatibility issues related to material science, biomechanics, and host responses. In this review, three issues that are highly pertinent to biocompatibility of joint replacements are examined. These topics include how implants initially osseointegrate within bone, potential adverse effects of byproducts of wear that can lead to aseptic loosening and perprosthetic osteolysis, and the potential for new bearing surfaces to extend the lifetime of implants. A clear understanding of these important issues will facilitate the development of novel strategies to improve the longevity and function of implants for joint replacement in the future. © 2008 Wiley Periodicals, Inc. J Biomed Mater Res 90A: 603–618, 2009

Key words: total joint replacement; biocompatibility; osseointegration; wear; osteolysis; alternative bearing surfaces

INTRODUCTION

Total joint replacements of the upper and lower extremities are some of the most efficacious, cost-effective interventions in all of surgery. These operations alleviate pain and improve function in a consistent fashion. For elderly patients, the survivorship of hip and knee replacements is greater than 90% at 15 years.[1] The future challenge is to devise joint replacing implants that will function for the lifetime of the patient without any activity restrictions or adverse sequelae. In order for this to be accomplished, important patient, surgical, and implant variables have to be optimized. Although issues related to patient selection and specific surgical technique are beyond the scope of this report, issues related to implant biocompatibility are of paramount importance and the topic of this review. In particular, three specific topics are highly germane to biocompatibility of joint replacements. These topics include initial osseointegration of implants, byproducts of wear that can lead to aseptic loosening and perprosthetic osteolysis, and the potential for new bearing surfaces to extend the lifetime of an implant.

Implants for joint replacement must integrate within bone for long-term performance. These implants must be stable to physiological loads; continued migration of implants is the hallmark of aseptic loosening. Osseointegration may be accomplished

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using cemented or cementless techniques. Immediately after implantation, articulating and nonarticulating surfaces begin to wear, and generate wear particles that are generally distributed locally (within the joint itself), regionally (for example to lymph nodes), and in some cases systemically. Particles and ions may have adverse effects, especially if the local mechanisms for dealing with these byproducts are overwhelmed. In particular, periprosthetic osteolysis may undermine the bone bed and compromise the stability of the implant. Idiosyncratic immune reactions may also occur. Newer bearing surfaces have been devised that have shown improved wear characteristics. However, with the introduction of new or enhanced materials, further issues have arisen, such as the generation of smaller particles. Overall, it is hoped that these newer articulations will extend the longevity of joint replacements and allow more normal function for younger more active patients.

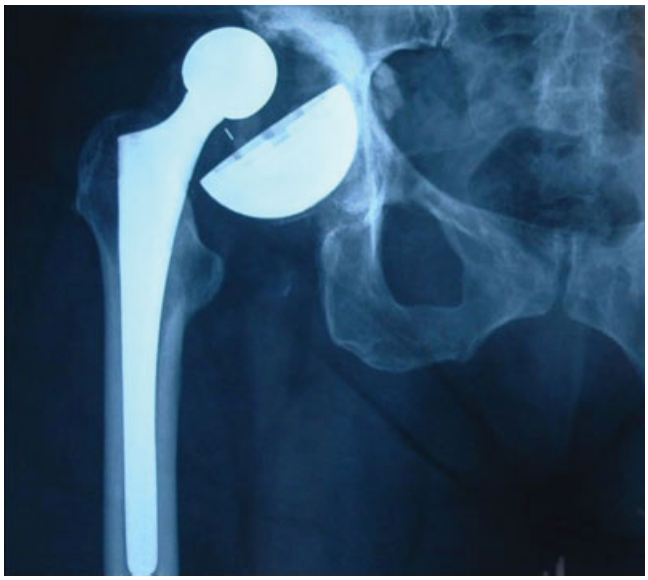

Figure 1. Total hip replacement with loose acetabular component. The cementless femoral component is stably fixed; however, the acetabular component has lost fixation and migrated. The femoral head has dislocated. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

OSSEOINTEGRATION OF ORTHOPEDIC IMPLANTS

Initial osseointegration of orthopedic implants

Implants for total joint replacement must obtain stable long-term fixation to bone in order to function normally.[2,3] If this is not accomplished early in the lifetime of an implant, then the joint prosthesis continues to migrate when subjected to physiological loads (Fig. 1). This progressive migration of an implant is painful and adversely affects the normal biomechanics of the artificial joint construct. Indeed, migration of an implant can be detected within the first 6–12 months after implantation using sophisticated techniques such as radiosterophotogrammetry and is predictive of late failure.[4,5]

Stability of an implant can be obtained by machining the bone bed so that the implant is directly impacted into bone initially with a tight fit, with little subsequent motion at the interface. The receiving bone bed is usually prepared to be slightly undersized (by 1–2 mm) compared to the implant, so that the prosthesis must be forcefully impacted into the cancellous bone in a "press fit" fashion. Alterations of the prosthesis surface by physical (such as with surface texturing or porous coating) or chemical means (such as with bioactive coatings and other molecules) attempts to provide a more long-lasting implant interface.

Stability of an implant within bone can also be achieved by using an intermediary filling material such as bone cement. These low modulus intermediary materials have no adhesive properties and simply function as a grout.[6] The advantage of this approach is that the receiving bone bed does not have to be machined as precisely, as the bone cement is used to fill in the incongruities between the prosthesis and the surrounding bone.

Osseointegration and biocompatibility

The potential advantages and disadvantages of cemented versus cementless fixation methods for prosthetic stabilization are debatable. However, both methods of fixation depend on the concepts of osseointegration and biocompatibility of the implant (and any intermediary materials) with the surrounding bone. The term "osseointegration" was originally coined by Bränemark et al. to describe what appeared to be direct contact of titanium implants with bone without any intermediary tissue.[7–9] Subsequently, the definition was changed to reflect a "direct structural and functional connection between ordered, living bone, and the surface of a load-carrying implant."[7,8] This definition was predicated on observations of specimens under the light microscope. More sophisticated techniques such as electron microscopy later demonstrated the presence of a thin intermediate molecular layer at the interface.[9] Recent discussions of the term osseointegration emphasize the specific physicochemical characteristics of the interface tissue and the functional aspects of the implant.[10] In particular, the interface between a prosthesis and bone must withstand high shear stresses to remain rigidly fixed; high interfacial shear

stress favors the differentiation of the intermediary tissues into fibrous tissue, rather than cartilage or bone.[11] Initial interfacial micromotion greater than about 50–100 μm has been shown to inhibit bone ingrowth.[12]

The term "biocompatibility" is also relevant to a discussion on implants for joint replacement. Materials that undergo osseointegration are usually biocompatible; however, this may not be the case, for example, when byproducts of a material cause adverse biological sequelae later on. Perhaps, the most acceptable definition of the term biocompatibility is the one offered by Professor David Williams in which biocompatibility is described as "the state of mutual coexistence between a biomaterial and the physiological environment such that neither has an undesirable effect on the other."[13,14]

The biology of osseointegration

When an implant is surgically placed within bone there are numerous biological, physical, chemical, thermal, and other factors functioning that determine whether or not osseointegration will occur. The initial surgical procedure causes local tissue trauma and bleeding; this stimulates an acute inflammatory response in bone and the surrounding soft tissues.[15,16] This leads to the ingress of proteins and cellular infiltrates composed primarily of polymorphonuclear leukocytes, macrophages, fibroblasts, and mesenchymal progenitor cells. These events are common to the first stage of fracture healing. Growth factors such as fibroblast growth factor, transforming growth factor β and other bone morphogenic proteins, insulin-like growth factor, vascular endothelial growth factor, and others stimulate the proliferation, differentiation, and maturation of osteoblast precursors. Autocrine, paracrine, and hormonal signaling mechanisms also stimulate the migration and maturation of osteoclastic precursors that resorb dead bony trabeculae and cellular debris. Acute inflammation may resolve and an initial lace-like trabecular bony layer then surrounds the implant. Alternatively, inflammation may persist and develop into a chronic phase with eventual fibrosis. Factors associated with chronic inflammation and fibrosis include poor local vascularity of the bone bed, interfacial motion (especially large shear forces), infection, prolonged allergic or foreign body responses, and chemical and thermal trauma. Over subsequent weeks and months, the trabecular callus surrounding implants undergoing successful osseointegration remodels to form a more consolidated mature structure that can transmit load more effectively. Stable implants that abut cortical bone can osseointegrate directly via mesenchymal osteoprogenitor cells from the marrow and endosteum. Stable implants with a fibrous or cartilagenous encapsulation layer can undergo so called "primary bone healing" directly, with metaplasia of the encapulation tissue to bone. Gaps at the implant-bone interface and continued instability impede osseointegration. Furthermore, this gap, an extension of the effective joint space provides a conduit for wear particles and other implant byproducts, and transmits waves of fluid pressure during cyclic loading of the prosthesis. The bone bed surrounding an implant undergoes constant remodeling through the lifetime of the patient, because of a disparity between the physical properties of the implant and the surrounding bone. This is primarily due to differences in the modulus of elasticity between bone and the (usually) stiffer implant. This may result in adverse bone remodeling, for example, when the proximal end of the femur becomes osteopenic years after a fully porous coated femoral component has been implanted.[17]

Facilitation of osseointegration of cementless implants

Initial implant stability can be increased by machining a "press fit" in the bone bed via underreaming, and by the use of adjunctive physical methods of fixation such as roughened surfaces on the implant, pegs, screws, splines, etc. These methods afford immediate physical fixation and are important to resisting micromotion and shear stresses at the interface. During implant osseointegration, micromotion, should be minimized or fibrous tissue will form.[18,19] If motion is excessive, a synovial-like lining layer will form at the interface.[20,21] Although porous coatings and roughened surfaces provide an immediate "scratch fit" with the surrounding bone, their overall efficacy depends in part on bone ingrowth and ongrowth that occurs at a later time, usually within the first few weeks to months after implantation.[16,19] For bone ingrowth, the optimal pore size has been determined to be about 50–400 μm.[22] The prosthesis characteristics, including the material type, implant fit and fill within bone, and surface characteristics including topography, chemistry, and energy are extremely important in determining implant stability and potential for osseointegration.[19,23–25]

Implant fixation can be further enhanced at a later time using biophysical stimulation. These methods include pulsed electromagnetic fields, low intensity pulsed ultrasounds, and other physical methods that increase the stress to bone.[26] These methods were first used to accelerate fracture healing but have shown promise with regards to improving implant fixation. Each skeletal site may require specific me-

chanical stimuli for improved implant fixation because of differences in bone shape, architecture, cellularity, vascularity, muscle mass, etc. The biophysical aspects of bone formation and degradation are integrated into a complex system involving the expression of numerous cytokines and growth factors, prostanoids, nitric oxide, and other molecules and pathways that regulate cell homing, proliferation, and differentiation. Recently, the molecular biological aspects of physical stimulation and enhancement of bone formation have been summarized.[27]

In addition, osseointegration may be enhanced with the use of bioactive coatings such as calcium phosphates, hydroxyapatite, glasses, and other materials.[28–31] These coatings function as an osteoconductive surface for osteoprogenitor/osteoblast cell attachment, proliferation, and differentiation. Bioceramic hydroxyapatite surfaces have been used successfully to coat orthopedic implants and can be deposited by different methods. These coatings are resorbed very slowly and are brittle. Thick coatings may shear or fail under fatigue and possibly become a source of third body wear. In some cases, attempts have been made to add growth factors to confer some degree of osteoconductivity to the coating. However, methods to deposit calcium phosphate coatings on metallic implant surfaces usually employ unphysiological conditions, such as very high temperatures that would denature proteins. Thus growth factors can only be superficially placed by absorption, by binding to other proteins or by chemical treatment, resulting in rapid release. Recently, more biomimetic coatings of calcium phosphate produced under physiological conditions can incorporate proteins directly into the inorganic lattice and release growth factors more slowly.[27] Other biomolecules are being examined in an effort to enhance osteoblast/osteoprogenitor attachment, proliferation, and differentiation to form new bone.[32,33]

Does osseointegration of cemented implants occur?

Bone cement has been used for over 40 years to stabilize implants within bone. Sir John Charnley and Dennis Smith popularized the use of polymethylmethacrylate in hip replacement and to this day nonbiodegradable bone cement with radio-opacifier additive is still widely used.[6,34] Despite traumatic, chemical and thermal trauma during insertion of a cemented implant and remodeling of the surrounding bone over time, cemented implants have proven to be very durable over the long term.

Polymethylmethacrylate is normally dissolved by organic solvents during routine processing of tissue specimens; however, large cement lakes, ghost-like spherical polymer remnants, and small particles of the radio-opacifier can be appreciated on histological sections of the implant-bone interface tissue of loose implants. In autopsy retrieval studies of well-fixed cemented implants, trabecular bone was seen to abut the cement with little intervening fibrous tissue. Indeed, Charnley thought that the fibrocartilaginous tissue that formed at the interface could undergo metaplasia to bone over time.[33] The surrounding bone often remodels, forming a secondary, circumferential, trabecular "neocortex" adjacent to the cement.[34,35] Once the cement fragments, periprosthetic osteolysis occurs due to a foreign body and chronic inflammatory response to the debris (Fig. 2).[36] Improved cementation techniques including thorough cleaning with pressurized saline and drying of the bone, the use of a cement restrictor and cement gun, prosthesis centralizers, and methods to rid the cement of stress risers using vacuum mixing improve the intrusion of cement into the bony interstices. If cement fatigue fracture or cement separation from the prosthesis (debonding) do not occur, cement may provide an intimate enduring interface with the surrounding bone.

Summary

Osseointegration of implants for joint replacement is a necessity for long-term pain-free function. Systemic and local host factors, implant materials and design, and surgical technique are all important aspects that determine the eventual success or failure of a surgical reconstruction.

WEAR BYPRODUCTS AND LOOSENING

Aseptic versus septic loosening

Even if implants for joint replacement are initially well integrated, the components may loosen if the fixation to bone is weakened by the foreign body reaction to implant-derived wear debris. This leads to late so called aseptic loosening.[37] Also septic loosening is a real threat, caused by implant-related infections, but is not subject of this chapter. Septic loosening has been defined using Robert Koch's postulates, which essentially state that to be able to called septic, one should be able to culture an infectious agent from patient samples. Lately, debate has been raised concerning whether living (proliferating) microorganisms are indeed necessary for septic loosening or could loosening be caused by microbial structures known as pathogen-associated microbial patterns (PAMP) recognized by pattern recognizing receptors (PPR), in particular Toll-like receptors (TLR).[38,39] In the gray zone between outright septic and aseptic loosening could still reside indolent bio-

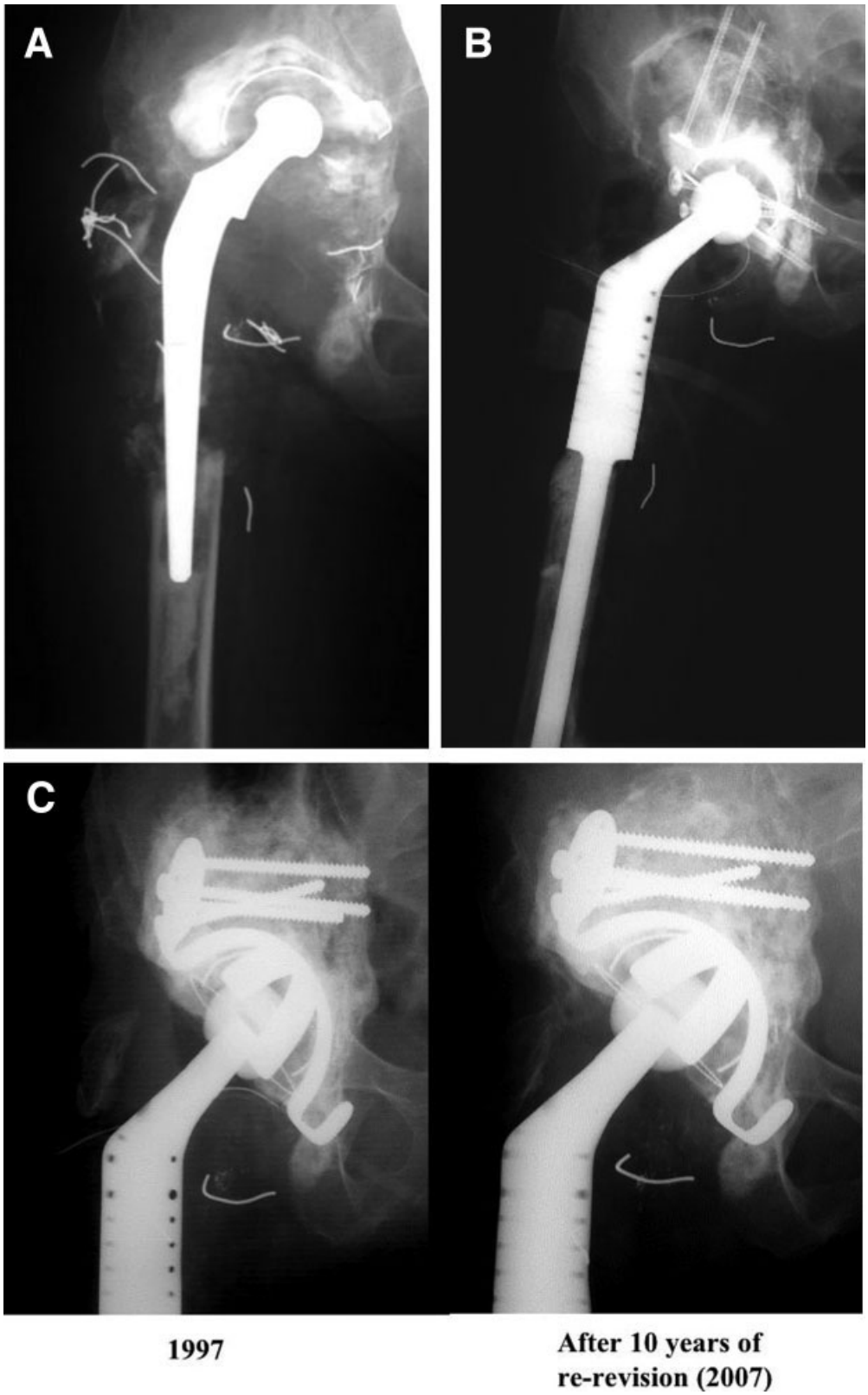

Figure 2. Massive periprosthetic osteolysis around a total hip replacement. This patient received a Charnley-type cemented total hip arthroplasty 16 years previously. She did not show up for follow-up until she felt severe pain with walking. Massive bone loss (periprosthetic osteolysis) was found in the proximal femur and acetabulum (A). Histological analysis of the tissues showed a foreign body reaction. The hip was reconstructed with a cemented megaprosthesis and impaction bone grafting on the femoral side, and structural allograft on the acetabular side (B). The acetabular reconstruction failed, but there was sufficient bone stock to then revise the socket again (C). This reconstruction appears sound 10 years later (C). (Figures courtesy of Dr. Masaji Ishii).

film associated "infections," in which microbes live serene *vita minima* hidden in the slime (extracellular polymeric substance) they have produced.[40,41]

Fluid pressure waves and the effective joint volume/cavity

In successfully osseointegrated implants, the junction between implant or cement surrounding it and host bone is a tight or bony union. In loosening the implant-host interface becomes dissected, probably in part due to fluid pressure waves and in part due to proteinases. The surgeon-made joint soon develops a synovial-like lining, which ultrafiltrates plasma and adds hyaluronan and more or less joint fluid specific components to it. Periodically, the volume of joint fluid may be increased due to inflammation, in part caused by wear byproducts and biomechanical stress, and as one of the consequences, the fluid volume increases. Fluid is not easily compressed and, therefore, fluid pressure waves are generated due to cyclic pressure variations in the hip joint fluid during walking, running, and other physical activities.[42] This has relevance to the foreign body reaction. Although wear debris is produced in the artificial joint articulation, implant-derived foreign body byproducts can be seen all around the implant as the particles have been "transported" there from the joint cavity and articulating surface with the synovial fluid.

Neutral endoproteinases

Osseointegrated or otherwise well-fixed implant-host interfaces are quite strong biomechanically. They can be weakened by proteolytic enzymes. It is envisioned that these proteinases are produced as a response to irritating and phagocytosable foreign bodies. Phagocytosis of foreign bodies, in contrast to "autophagocytosis" of apoptotic "self" bodies, is coupled to inflammation. The professional phagocytotic cells, in aseptic loosening mostly inflammatory mononuclear phagocytes (monocytes/macrophages), become activated and produce oxygen and nitrogen radicals as well as proteinases. Proteinases released into the phagolysosomes are usually acidic cysteine or aspartic endoproteinases. This refers to the fact that their pH optimum, like that of pepsin, is acidic. In contrast, neutral endoproteinases are produced for export and have been considered to play a major role in the extracellular space. It is thought that under physiological conditions "physiological" pH close to 7.4 prevails. Indeed, it has been described that mononuclear phagocytes and foreign body giant cells produce excessive amounts of collagenases and other matrix metalloproteinases. In concert, they are able to degrade all components of the extracellular matrix, including that integrating the implants to host tissues. Therefore, proteinases such as MMP-1 (collagenase-1, fibroblast collagenase, tadpole collagenase), MMP-8 (collagenase-2, either neutrophil collagenase or mesenchymal isoform of MMP-8), MMP-13 (the major collagenase in rodents, which lack MMP-1), MMP-14 (the first membrane-type or membrane-bound MMP, MT1-MMP), and other MMPs with collagenolytic potential are produced,[43] released, and apparently activated to weaken the implant-host interface to mediate loosening and increase the effective joint space, which enables transport of foreign bodies from their site of production in the articulation.

Attention has also been drawn to neutral serine endoproteinases, such as elastase and cathepsin G, in loosening.[43] They can be found in aseptic loosening, but as they are richly present in the primary or azurophilic granules of neutrophils, they might play a particularly important role in septic, Toll-like receptor driven loosening although this is still open to debate.

Acidic endoproteinases

Although it has been supposed that the pH in the peri-implant tissues is "physiological," a question can be raised how physiological then is this artificial internal environment. This has been tested using direct pH measurements. It was found the pH in the peri-implant tissues is quite low, such that that the acidic cysteine endoproteinase cathepsin K could become autoactivated.[44] Cathepsin K was first found to be the major proteinase of osteoclasts. It is generally considered to be responsible for bone collagen degradation in the acidic Howship lacunae after HCl-mediated dissolution of the bone hydroxyapatite mineral. In an inborn or acquired cathepsin K deficiency, bone remodeling is dramatically disturbed and osteopetrosis (marble bone disease) results. This condition is known as pycnodysostosis as the affected patients due to deficient enchondral bone formation and remodeling have a short stature (the famous painter Henri de Tolouse-Lautrec had this disease). Later cathepsin K has been found also in other cells, including macrophages, osteoblasts, and fibroblasts. Auto-activated cathepsin K in the acidic peri-implant milieu has been found in high concentrations in peri-implant fluid and tissues.[45] Therefore, it could be responsible for the weakening of the implant-host interface and increase in the size of the effective joint volume. It is not clear at present to what extent MMPs and cathepsin K mediate normal soft tissue remodeling versus tissue destruction contributing to loosening.

Chemokines and cytokines

One other important consequence of the foreign body and inflammatory reaction is local production of chemokines and cytokines.[46,47] In *in vitro* tests usually a fixed number of cells is subjected to wear particles, and chemokine and cytokine production are assessed. *In vivo* the situation is more complex as the active events in the synovial membrane-like interface are amplified by recruitment of more cells. This includes induction of sticky selectins and vascular endothelial cell adhesion molecules, transmigration of immigrant inflammatory mononuclear cells,[48] and local cellular proliferation and recruitment of so called "resident" cells to the area of inflammation. Earlier the role of "structural" cells such as vascular endothelial cells, fibroblasts, osteoblasts, adipocytes, neurones, and mast cells was not recognized. Particularly important in this reaction are proteinases and osteoclastogenic factors produced by mesenchymal-derived cells, including fibroblasts and osteoblasts.[49] Fibroblasts normally produce the structural strength providing collagen fibres, but need to have the cellular machinery for remodeling. Although these cells are not professional phagocytes but pinocytosing cells, they can be recruited and/or activated by the "proinflammatory" cytokines produced by the foreign body and phagocytosis activated leukocytes.[50]

Osteoclastogenesis and formation of foreign body giant cells

Another detrimental consequence of a foreign body reaction is the fusion of macrophages into osteoclasts or foreign body giant cells, which belong to the phagocyte family. Relatively early, it was observed that some type of direct contact between osteoblast and osteoclast precursor can induce the formation of multikaryons. This process was intuitively considered to be regulated by a balance between catabolic and anabolic cytokines and growth factors. It was first when receptor activation of nuclear factor kappa B ligand (RANKL) and its receptor RANK were found when clarity was achieved[51] (Fig. 3). RANKL is found on the surface of mesenchymal-derived cells, including osteoblasts (which may stimulate osteoclastogenesis) and fibroblasts (which may stimulate the generation of foreign body giant cells). In this respect, a direct cell contact still would seem to be important. On the other hand, RANKL can also be solubilized by "sheddases" or produced in soluble form[52] In high concentrations and *in vitro* macrophage-derived multikaryons can be generated by soluble RANKL molecules alone. *In vivo* direct cell-to-cell contact may be more important as the potent RANKL-RANK interaction needs an effective control mechanisms and that is attained by a soluble RANKL receptor known as osteoprotegerin (OPG). OPG protects bone against RANKL-driven osteoclastogenesis and osteolysis. The very rich presence of foreign body giant cells, foreign body granulomas, osteoclasts, and peri-implant osteolysis verify for the role played by this system in aseptic loosening although the chain of events leading to this unfortunate outcome is still somewhat unclear.

Scavenger receptors

Even unopsonized wear debris can be phagocytozed by phagocytes. These cells utilize scavenger receptors (SR) which may belong to SR-A or -B or some other of the now known eight human scavenger receptor families.[53] In internal medicine, they are best known as receptors for oxidized low density lipoprotein and in orthopedics for uptake of implant wear debris. Such receptors enable phagocytosis of unopsonized self or nonself foreign bodies. This is possible as they must have, to be able to scavenger "waste," a relatively broad receptor specificity. Their ligand or "cargo" does not need to be covered by opsonizing antibodies or complement, but can be phagocytozed anyway. An example of such SR in the peri-implant tissues is MARCO (macrophage receptor with collagenous structure), which belongs to SR-A family scanvengers (Ma G, personal communication). Early on during the aseptic, debris-driven loosening these scavengers may play an important role. In addition, because of their broad specificity for both self and nonself, they also belong to the PPR, of which already TLRs were mentioned above. Scavenger receptors may or may not be coupled to inflammatory cell responses, such as oxygen radical production and cytokine and proteinase synthesis and secretion, meaning that they are coupled to important cell regulatory signal transduction pathways. In patients with aseptic loosening, phagocytosis of implant-derived foreign bodies is coupled to inflammatory host responses, whereas autophagocytosis of apoptotic bodies or even phagocytosis of implant-derived foreign bodies may be uncoupled from these inflammatory responses for somewhat unclear reasons. T lymphocyte activation and associated interferon-γ (IFN-γ) production may occur as a result of hapten-modified self, or microbe-derived PAMPs could be another reason, and cross-reactions between triggers (such as exogenous infectious agents) and endogenous ligands (such as implant-derived particles) could represent yet another.

Delayed-type hypersensitivity

Another important aspect relates to the potential cell-mediated immune reactions may play when

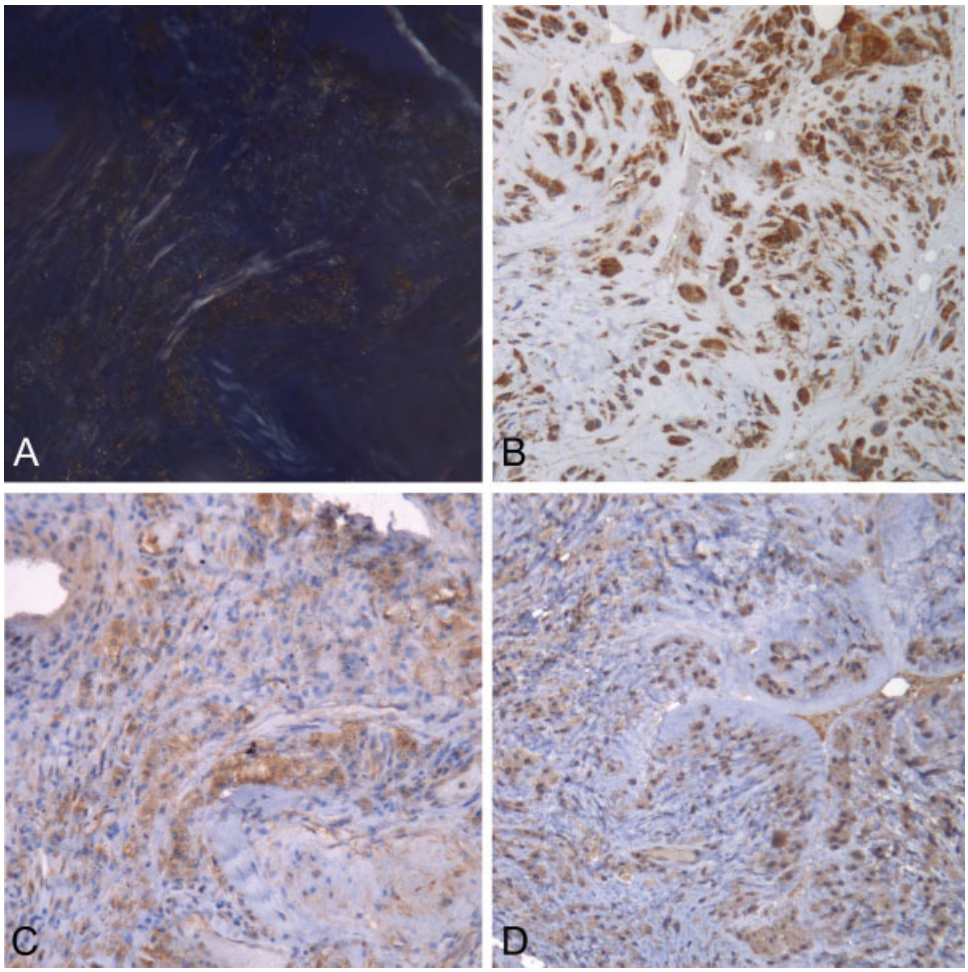

Figure 3. Foreign body reaction to polyethylene particles in periprosthetic tissue. Panel A is a tissue section prepared from the peri-implant synovial membrane-like interface tissue showing positively birefringent polyethylene particles under polarized light microscopy. Larger polyethylene particles are seen under this magnification as relatively bright birefringent particles, whereas the small submicron-sized particles can not be visualized. Particles are found embedded in the extracellular matrix and inside local mononuclear cells. Panel B shows numerous CD68 positive macrophages (brown staining areas). Panel C shows activated macrophages that express Tumor Necrosis Factor alpha (TNFα), a key proinflammatory cytokine. Panel D shows numerous receptor activation of nuclear factor kappa B ligand (RANKL) positive mesenchymal cells. These cells and this molecule are key stimuli for the formation of multinuclear foreign body giant cells (foreign body reaction) and osteoclasts (peri-implant osteolysis) from pre-fusion macrophages. Panels B and C: Immunoperoxidase staining with monoclonal antibodies, counterstained with hematoxylin. ×100 magnification. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

reactions against metal ions are produced.[54,55] Corrosion always occurs when metallic implants are placed in the human body. Electrochemical dissolution of metal ions is an important source of implant-derived debris in particular with metal-on-metal articulations. This is due to the fact that the size of the foreign body particles produced in such articulations is very small, which inevitably increases their surface. This accelerates corrosion, so much so that such implants are not recommended to patients with renal failure or to women of child-bearing age. In other patients, these metal ions may bind to "self" proteins and modify them so that they are recognized as "nonself." As these new hapten-protein complexes were never before introduced to the immune system, reactive T lymphocyte clones exist in the multitude of at least 10^8–10^9 different T cell receptor specificities or "keys," one or some of which fit to the "nonself" lock leading to an antigen-driven oligoclonal T cell activation. This has been described to be associated with more severe and rapidly progressive aseptic loosening. The most likely mechanism is that the activated T lymphoblasts produce IFN-γ locally, which sensitizes the local monocyte/macrophages so that they start their harmful aggression against foreign bodies.[56]

TABLE I
Biocompatibility of Implants and Their Byproducts

Size of the Particle	Mechanism of Formation	Destiny in the Peri-implant Tissues	Examples of Host Responses Elicited
Bulk (macroscopic)	Initially industrially produced	Substrate for the peri-implant cells	Implant capsule formation or osseointegration
Large (tens of microns)	Microfractures	Embedded in the extracellular matrix or trapped between the gliding surfaces	Isolated to granulomas or causing third body wear
Moderate (between submicron and several micron size)	Wear	Embedded in the extracellular matrix or phagocytozed	No response or foreign body reaction
Small (several nanometers)	Wear	Floating in the extracellular matrix/ interstitial fluid or pinocytosed	May not elicit a response or may increase the attachment area for, that is, lipopolysaccharides
Very small (metal ions)	Corrosion	Haptenic groups	Delayed type hypersensitivity, remote effects, that is, nephrotoxicity

According to the ISO standard, a biocompatible implant should be tolerated as is but also what it may turn into in the human body; this does not always occur.

Does the size matter?

It is often discussed if the size of particles matters; in implant wear and loosening it seems to matter. This has been summarized in Table I. The effect of biomaterial in the human body varies from cell and tissue friendly substrate to irritating 0.7–1.0 μm size phagocytosable particles to tiny metallic ions which can initiate and maintain delayed-type IV hypersensitivity reactions. An interesting question relates to nanoparticles less than 500 nm in size, which are in nonaggregated, singular form endocytosed via pinocytosis rather than phagocytosis. As metal-on-metal articulations, which volumetrically produce perhaps some 50× less wear debris, but in 10× higher numbers than metal-on-UHMWPE articulations, rarely lead to chronic foreign body reactions, the preliminary speculation would be that it is not, but this requires more research. One caveat related to the small size of the wear debris is perhaps the high corrosion and absorption surface developed that way. It can be calculated that if 1 cm^3 of a cube is divided to 1 nm^3 particles, the total surface area increases 10^7 fold.

Summary

The effects of implant-derived foreign bodies on loosening are quite well understood at the macro- and micro-level, but the effects at nano- and molecular-level are somewhat unclear. Also hydrophobicity and surface energy of the implant-derived particles and various microbe-derived foreign bodies and PAMPs need more research for better understanding of the biological principles which would hopefully translate into improved clinical outcomes.

NEW MATERIALS-ULTRAHIGH MOLECULAR WEIGHT POLYETHYLENE

Ultrahigh molecular weight polyethylene (UHMWPE), the basic and reliable interposition material in total joint replacement, faces significant challenges since the last decade (Fig. 4). The rise of alternative bearings, such as metal-on-metal and COC articulations at the hip, and the threats of oxidation, wear and material fracture, have fostered academic and industrial research to determine the role of this material in the future of total joint replacements.

First generation highly cross-linked polyethylenes

While increased wear resistance has been confirmed in the so-called highly cross-linked polyethylenes (HXLPEs) both *in vitro* and *in vivo*, irradiation required for this cross-linking (whether by the time consuming gamma irradiation or by the high energy electron beam irradiation that requires a more costly set-up) generates alkyl free radicals within the material.[57] These free radicals, present in the amorphous phase, but stored in crystals and reacting with oxygen at the amorphous-crystal interface, foster material oxidation. This was an important concern as material oxidation was detected in UHMWPE prosthetic components stored on the shelf (particularly if packaged in air) before implantation. Recently, oxidation has been also detected after implantation, progressing within the material during *in vivo* use.[58] Oxidation while the implant is on the shelf has been decreased with barrier packaging after irradiation performed under vacuum or an inert atmosphere (N2, He, Ar, etc.) but not vanished, thus limiting the

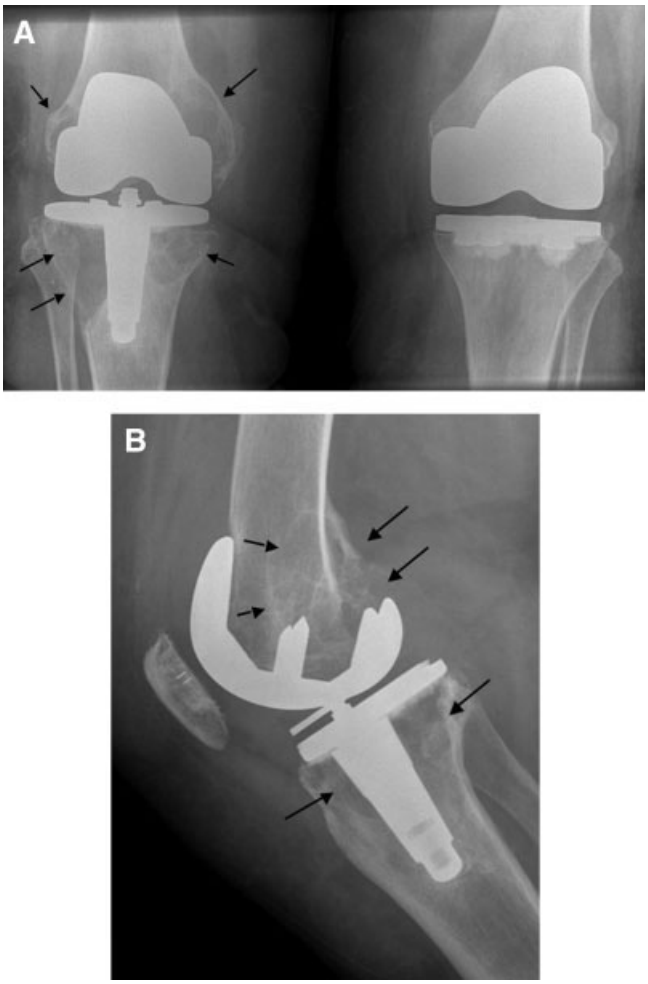

Figure 4. Severe periprosthetic osteolysis around a total knee replacement. There is severe femoral and tibial periprosthetic osteolysis (arrows) around the right total knee replacement due to polyethylene wear particles. The left total knee replacement is well fixed. (A) anteroposterior view; (B) lateral view of the right knee.

recommended storage time to a maximum of 5 years. However, *in vivo* oxidation in the highly oxidant inner body ambiance is unavoidable, and different manufacturing processes aim to minimize it.

The menace of free radicals has been confronted in the so-called first generation HXLPE by post-irradiation thermal treatments. Two different methods, annealing and remelting, with proprietary differences by the main orthopedic manufacturers, have been used in this first generation process. Annealing techniques are based on polyethylene heating under the fusion (melting) temperature that usually starts at 120–130°C. Then, polyethylene crystals are not melted and the structure and crystallinity of the material is basically conserved, albeit traces of free radicals may remain. Remelting processes intend to remove free radicals by melting the polyethylene crystals in whose surface free radicals are present. This requires temperatures greater than 140–150°, followed by material cooling that generates recrystallization. Final crystallinity may be different from the original material and, after structural changes, mechanical properties may also differ. Down sides of both thermal treatments have been confirmed *in vivo* by retrieval studies, where annealed material showed ongoing oxidation[59] but closer mechanical properties to original UHMWPE, and remelted material, with minor oxidation, showed a certain decrease in fracture and fatigue resistance[60] that may affect particular design features with thin polyethylene areas or stress concentration. Although clinical results in the mid-term follow-up demonstrated a decrease in the wear rate,[61,62] retrieval findings in the first generation HXLPE confirmed that the focus to decrease UHMWPE failure should be not only directed to wear, but to oxidation and mechanical properties.

Oxidation is detected by destructive methods both in retrieved and nonimplanted UHMWPE components. Sections of 100- to 200-μm thick undergo FTIR (Fourier Transformed InfraRed spectroscopy) analysis to define the oxidation index, where the peak of ketone species (at wave number 1718 cm^{-1}) compared to a reference peak (1370 cm^{-1}) permits a quantification of the material's oxidative status.[57] A norm to calculate the index can be found in ASTM F2102-01. However, a more relevant question is the detection of oxidation potential within the material, and hydroperoxide determination (detected at wave length 1630 cm^{-1}) has been used for this purpose.[63] Findings of oxidation potential in first generation HXLPE, after either annealing or remelting, prove the need for so-called second generation of HXLPEs.

Second generation highly cross-linked polyethylenes

The aim of this second generation is to maintain or even decrease the low polyethylene wear rate of the first generation HXLPE while maintaining satisfactory fracture and fatigue resistance of the material and, finally, to decrease or eliminate material oxidation. It has been claimed that oxidation is controlled in the commercially available HXLPE of the second generation treated with sequential annealing. The rationale behind this material is to progressively obtain a HXLPE while controlling the free-radical production by repeated annealing cycles. *In vitro* data supports decreased oxidative damage under artificial aging protocols,[64] increased wear resistance, and satisfactory material mechanics.[65] Clinical use or trials will have to provide *in vivo* results to support or refute this claim.

Another second generation HXLPE strategy under research is the use of oxygen scavengers within the material. Hydrogen transfer but also electron transfer mechanisms have antioxidant effects. Vitamin E (α-tocopherol), a natural antioxidant can donate a hydrogen atom to reduce free radicals and broadly used in the food industry with a well-confirmed human body tolerance, is the main proposal under research, followed by nitroxides. Vitamin E has been blended to the material resin before UHMWPE consolidation, or has been introduced by diffusion during the melting of the material, at a concentration ranging 100 to 500 ppm. Laboratory results confirm that Vitamin E diffuses to the inner material after doping during subsequent homogenization in an inert gas,[66] and that the oxidation potential of UHMWPE containing vitamin E is virtually nonexistent. Furthermore, trace concentrations of Vitamin E (under 500 ppm) do not interfere with UHMWPE cross-linking,[67] whereas higher concentrations decrease cross-linking density. Laboratory tests have shown that the addition of Vitamin E improves wear resistance and fatigue performance.[68] Thus, the potential of this new strategy generates great expectations regarding oxidation control, although this material is not commercially available at present.

Other research proposals to modify UHMWPE have been directed towards the maintenance of mechanical properties, and include surface modification with N or He ion implantation, nanocomposite reinforcements through multiwalled carbon nanotubules, or 2-methacryloyloxyethyl phosphorylcholine polymer grafting.[69] Intensive research in this area will prove the real value of these and other possibilities, but predicts further improvements to further extend the longevity of total joint replacements based on UHMWPE as the interposition material.[70]

NEW MATERIALS-BIOCERAMICS

A different strategy to decrease wear products and subsequent osteolysis, particularly in total hip replacements, is the use of ceramic-on-ceramic (COC) articulations. The concept has been in use for more that 35 years,[71] and satisfactory long-term results of early series[72] proved the value of this approach. The extreme hardness of the material with high scratch resistance, together with a low friction coefficient linked to favorable lubrication due to improved wetability made this coupling a successful artificial joint. The few generated particles also showed a reduced reactivity with surrounding tissues in the appropriate size range,[73] and these particles did not seem to cause aseptic loosening.[74] However, early ceramics with failed designs exhibited ceramic fracture and striped wear related to modular junctions, couplings, and material issues such as large grain sizes of alumina ceramics.[75]

Efforts were directed towards material improvements, and zirconia was proposed to substitute for alumina as the coupling ceramic. However, an unacceptable wear rate in zirconia-zirconia couplings,[76] related to small grain and wear particles that provoked increasing wear, led to discontinuation of this articulation, although zirconia on polyethylene is still in use.

Second-generation alumina-on-alumina materials and designs corrected some of the detected problems, and the estimated risk of ceramic head fracture currently is very low.[77] Controversy remains because of significant intraoperative constraints due to the material selection, particularly the problem of impingement. Impingement may occur between ceramic and titanium because of femoral neck notching, and this may lead to dislocation or femoral neck fracture. Also, COC articulations may be associated with striped wear, which is related to component orientation, and friction. Furthermore, a "squeak," namely an unpleasant noise may occur in COC articulations, and may necessitate revision to a different bearing couple.

While currently used for ceramic-on-polyethylene articulations, the use of ceramics on pure COC couples is frequently restricted to a young population in whom low wear rates are necessary to extend the life of the implant. As controversy remains regarding the potential for fracture and impingement, present efforts on COC research has lead to the development of composite ceramics, where both wear and fracture resistance are optimized.[78]

NEW MATERIALS-METALS

Metals and their alloys are used as biomaterials because of their excellent mechanical properties as well as electrical and thermal conductivity, and corrosion resistance. Metals such as iron (Fe), chromium (Cr), cobalt (Co), nickel (Ni), titanium (Ti), tantalum (Ta), niobium (Nb), molybdenum (Mo), aluminum (Al), vanadium (V), and tungsten (W) have been used to make alloys for manufacturing implants. Although some metallic elements are essential and exist as naturally occurring forms, that is, Fe for blood cell function and Co for synthesis of vitamin B_{12}, metals cannot be tolerated in large amounts in the body and cause harmful reactions.[79]

Byproducts of metals

Stainless steels, CoCr-, and Ti-based alloys are currently available as metallic materials for supportive and/or articulating sites of joint replacements. The biocompatibility of metallic implants for joint replace-

ment is of great concern because these implants can corrode *in vivo*. The association of metal ions and organ toxicity, cancer, and delayed hypersensitivity of patients undergoing total joint arthroplasty is a frequent topic of research and speculation. It is well known that wear debris from metallic implants can evoke unfavorable local host response in the periprosthetic tissues, leading to osteolysistic and implant failure.[80]

Corrosion, a gradual degradation of metallic biomaterials by electrochemical attack, occurs in the environment of the human body. The metal is oxidized, resulting in the formation of metal ions and release of electrons in the process of the reaction, leading to material loss. The metallic materials for biomedical use are self-protected by the spontaneous formation of a thin oxide layer. This passive film can act as highly-protective barrier between the metal surface and the aggressive biological environment, although the layer is only a few nanometers. The passive oxide layer decreases metallic dissolution to a low rate. However, unfavorable metallic dissolution by corrosion is accelerated at the site of localized breakdown of the oxidation layer. Different types of corrosion have been described as pitting, crevice, galvanic and fretting. Pitting corrosion is a type of localized corrosion caused by local dissolution of the passive film and the formation of cavities surrounded by an intact passivated surface.[81] Crevice corrosion is a type of localized corrosion closely related to pitting corrosion, and occurs preferentially in regions on the metal surface where mass transfer is limited, such as in narrow crevices or under deposits. Galvanic corrosion occurs when metals with different potentials are in direct contact in corrosive solutions or atmospheres. Fretting corrosion is a form of damage which occurs at the interface of two closely fitting surfaces subjected to slight oscillatory slip and joint corrosion action. Fretting corrosion, alone or in combination with crevice corrosion, has been recognized as one of the most important factors in implant corrosion.[82,83]

Metal-on-metal articulations

Metal ion release has recently been debated intensively in the clinical area related to metal-on-metal articulation. Modern metal-on-metal designs with polished Co-Cr alloy showed decreased wear compared to traditional metal-on-polyethylene designs, but lead to increased metal ion levels in blood and urine, even in patients with well-functioning implants.[84,85] Mulfunctioning devices may put the patient at considerable risk.[86]

Metal on metal couples made of CoCrMo alloy originated as Metasul® in 1988 and achieved successful clinical results.[87] Metal-on-metal articulations have advantages over metal-on-polyethylene bearings including a decreased wear rate of 50–100 times,[88] linear wear of 40 times and volumetric wear of 200 times.[89,90] Because of such low wear rates, the incidence of osteolysis is rare.[91,92] Metal-on-metal combinations also allow use of the larger femoral heads, which can improve stability and range of motion, provide superior lubrication, and avoid the risk of fracture of the bearing.

For metal-on-metal articulations, CoCr28Mo6 alloys (ASTM F799 and ASTM 1537, ISO 5832-12) are currently used. They differ in their content of carbon. High-carbon alloy contains >0.2 wt %, and low-carbon <0.07 wt %.[92] Low-carbon-on-low-carbon and low-carbon-on-high carbon combinations showed higher wear rate.[93,94] This contributes to higher numbers of particles and induces periprosthetic osteolysis around implants. However, low-carbon-on-low-carbon and low-carbon-on-high-carbon combinations, have demonstrated satisfactory clinical results with some exceptions.[91,92,95,96]

In spite of the clinical success of metal-on-metal articulations, there are disadvantages including possible biologic and carcinogenic concerns of increased metal ions especially in the patients with renal failure and in women of childbearing age.[92,97] Possible risk of hypersensitivity to metals has also been reported.[55,92,98] It seems reasonable to conclude that low-carbon metal-on-metal articulation produce inferior clinical results probably due to increased wear in comparison to that of high-carbon bearings.[99]

Improvement of the interface between metal and bone is another great interest. Alkali- and heat-treatments of titanium alloy are currently undergoing clinical trials to obtain better cementless fixation of acetabular and femoral components. This offers stronger bone bonding and a higher interlocking mechanism compared to conventional interlocking mechanisms, thus contributing to better osseointegration at the site of cementless fixation of titanium alloy implants.[100]

Metallic stems

Polished tapered cemented stainless steel femoral stems with a double taper structure yielded longer survivorship with fewer complications including intraoperative fracture, stem subsidence, thigh pain, and stress shielding, which appeared more frequently with cementless stems. The success of these cemented stems is probably due to the taper slip concept design with rotational stability, combined with modern cementing technique. Such stems can have a shape closed fixation design, meant to be contained by the cement mantle, or a force closed fixation design, relying on subsidence under load as a method

of maintaining stability. Force closed fixation can achieve favorable load transfer from stem to cement and bone, minimize cement debris and metal corrosion at the cement stem interface.[101,102] This design yielded superior survivorship even in the revision situation.[103] The polished tapered stem has been strengthened with the use of CoCr-based alloys instead of surgical stainless steel,[104] which gives much better corrosion resistance and mechanical advantages of the stem within a small-sized femur. One of the promising approaches is high quality amorphous diamond coating. Diamond has low friction, high resistance to corrosion, and enhanced bonding to bone. It is nonirritating, does not cause allergic reactions, and possibly has a lower potential risk of organ toxicity, DNA damage, and carcinogenicity by corrosion products. It is anticipated that diamond coating technology may improve osseointegration, decrease corrosion at the articulation, and at other locations including screw holes, the bone cement-metal interface and areas of neck impingement.[105,106]

THE FUTURE

Despite current success, the future challenge for joint replacement procedures is to devise a construct that will closely emulate the normal joint in a pain free manner, allow full, unrestricted activities, and last the lifetime of the patient. Ideally, the surgical procedure should be accomplished with only minor pain and minimal "downtime." Current total joint replacements do not meet these lofty aspirations, especially for younger more active patients. However, recent advances including the introduction of improved, more corrosion resistant materials, novel bearing surfaces with larger femoral heads, enhanced surgical techniques, and accelerated rehabilitation protocols hold great promise.

Patients are living longer and are engaging in more physically demanding lifestyles. Total joint replacement is being offered to both younger and elderly patients as a means of preserving mobility and independence. Can current technology keep up with the increasing needs and demands of this population? Clearly, this question cannot be answered at this time, because long-term follow-up has not been documented for the newest technologies that have recently been introduced. However, with databases and national registries with clearly defined outcome variables, and comprehensive analysis of failed retrieved implants, we can begin to understand what works (and what does not) and begin to design the next generation of implants accordingly.

Current needs include strategies to hasten implant osseointegration, perhaps with biologically based implant coatings, and more wear- and fatigue-resistant bearing surfaces and implants. Byproducts from implants need to be nontoxic and easily dealt with by known biological mechanisms. The surgical procedure needs to be simplified so that surgeons can safely and reproducibly perform these operations with a low incidence of complications and adverse events. Implant design has to be optimized so that adverse bone remodeling is minimized. These goals demand continued collaboration between basic and clinical researchers in biology, engineering and material science, and the clinical sciences.

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