Biomedical Technology Group, Department of Applied Physics,
University of Kuopio and
Department of Orthopaedics and Traumatology,
Helsinki University Central Hospital, Helsinki, Finland

Compatibility of the totally replaced hip

Reduction of wear by amorphous diamond coating

Seppo Santavirta

ACTA ORTHOPAEDICA SCANDINAVICA SUPPLEMENTUM NO. 310, VOL. 74, 2003

Cover illustration by Sam Vanni reproduced with permission from
”KUVASTO upphovsrättsföreningen för visuella konstnärer rf”.
Printed in Sweden
Wallin & Dalholm
2003

Contents

Abstract

Particulate wear debris in totally replaced hips causes adverse local host reactions. The extreme form of such a reaction, aggressive granulomatosis, was found to be a distinct condition and different from simple aseptic loosening. Reactive and adaptive tissues around the totally replaced hip were made of proliferation of local fibroblast like cells and activated macrophages. Methylmethacrylate and high-molecular-weight polyethylene were shown to be essentially immunologically inert implant materials, but in small particulate form functioned as cellular irritants initiating local biological reactions leading to loosening of the implants. Chromiun-cobalt-molybdenum is the most popular metallic implant material; it is hard and tough, and the bearings of this metal are partially self-polishing. In total hip implants, prerequisites for longevity of the replaced hip are good biocompatibility of the materials and sufficient tribological properties of the bearings. The third key issue is that the bearing must minimize frictional shear at the prosthetic bone-implant interface to be compatible with long-term survival. Some of the approaches to meet these demands are alumina-on-alumina and metal-on-metal designs, as well as the use of highly crosslinked polyethylene for the acetabular component. In order to avoid the wear-based deleterious properties of the conventional total hip prosthesis materials or coatings, the present work included biological and tribological testing of amorphous diamond. Previous experiments had demonstrated that a high adhesion of tetrahedral amorphous carbon coatings to a substrate can be achieved by using mixing layers or interlayers. Amorphous diamond was found to be biologically inert, and simulator testing indicated excellent wear properties for conventional total hip prostheses, in which either the ball or both bearing surfaces were coated with hydrogen-free tetrahedral amorphous diamond films. Simulator testing with such total hip prostheses showed no measurable wear or detectable delamination after 15,000,000 test cycles corresponding to 15 years of clinical use. The present work clearly shows that wear is one of the basic problems with totally replaced hips. Diamond coating of the bearing surfaces appears to be an attractive solution to improve longevity of the totally replaced hip.

Key words: - total hip replacement, - materials, - amorphous diamond.

Introduction

The system of Charnley's original low-friction arthroplasty was based on polyethylene acetabular and metallic femoral components attached to bone with the use of methylmethacrylate. Today the number of total hip replacements done worldwide exceeds 500,000/year. From the beginning, this concept was clearly more successful than several previous trials that failed because of poor design and often disastrous biocompatibility. The reported survivorship of Charnley low-friction arthroplasties ranged from 65% to 84% at 20 to 30 years (Callaghan et al. 2000, Brown et al. 2002). Early metal-on-metal McKee-Farrar total hip replacements have shown survivorship ranging from 53% to 89% at 10 to 15 years (Brown et al. 2002). However, eventually it became clear that even in the best series, total hip components gradually tend to become loose, with aseptic loosening still the single most important complication of total hip replacement (Harris 1994). Close association seems to exist between wear rate and osteolysis in total hip replacement (Dumbleton et al. 2002). The adverse effects of continuous mechanical loading in the loosening process have been emphasized, and for many years it was thought that methylmethacrylate and polyethylene debris were of a benign nature (Editorial, Lancet 1990). When periprosthetic osteolysis was first recognized, it was hypothesized that it was caused by a chronic low-grade infection. More recently it has become clear that extensive lysis also may appear around mechanically well-fixed total hip components in the absence of infection (Goldring et al. 1993). With time, methylmethacrylate and especially its wear products were found to be the cause of local adverse host reactions toward the total hip replacement complex (Jones and Hungerford 1987). The wear-products also cause third body wear in the bearings (McKellop 1998). However, periprosthetic lysis soon was noticable also in the uncemented total hip replacements where the production of polethylene wear particles is similar to that in cemented total hip replacements (Santavirta et al. 1991). It became clear that not only the periprosthetic synovial-like membrane but also the pseudocapsule contains biologically multipotent and active cells that produce chemical substances contributing to prosthetic loosening (Takagi 1996).

To date, many different materials have been tested to reduce wear and the generation of submicron-sized particles. Corrosion and ionic-type wear products are also important factors in the longevity of total joint replacement. At the same time, the implant materials have to undergo examination for their biocompatibility. For example, titanium, which commonly is used in uncemented total hip replacements, is very biocompatible in bulk form, but is at the same time soft and wears extensively, causing massive metallosis (Wright and Goodman 1995). Chromium-cobalt-molybdenum, although hard and comparatively wear-resistant, produces wear particles more locally toxic than those of Ti. Trials to improve methylmethacrylate cement have not been very successful, and many experiments with new polyethylenes and innovative designs have failed (Huiskes 1993).

Currently, several research groups study the material properties and tribology of total hip designs and materials. Simulator testing of new bearings (McKellop 1998), artificial aging of polyethylenes (Li and Burstein 1994), and Scandinavian hip registers (Herberts and Malchau 1997, Puolakka et al. 1999, Havelin et al. 2000) are examples of effective approaches to study materials and the function of total hip replacements. Predicting and evaluating the long-term performance of new or modified designs is a challenging subject at the forefront of orthopedic research today (Walker 2000). Clearly, metal-on-metal designs have become popular again (Schmalzried et al. 1996), new highly cross-linked polyethylenes seem promising (Muratoglu et al. 1999), and various coatings or surface treatments are undergoing experimentation (Lappalainen et al. 1998). Regarding new materials, diamond coating of metallic components to reduce wear and to provide more biocompatible prosthetic surfaces has been shown to be promising.

Concurrently, the large Scandinavian national hip registers reveal that Charnley low-friction arthroplasty still has one of the best 10-year records in large populations. Great effort is required to improve a component that already is very good. Regarding the huge and still increasing numbers of total hip replacements at risk of becoming loose, research to improve the biocompatibility, tribology, and durability of total hip replacements seems worthwhile (Santavirta 1998). The hypothesis is that amorphous diamond in particulate form appears to be inert and likely to cause only a low-grade host-response reaction. Tribological studies should clarify the potential of such amorphous diamond coating for THR bearings.

Purpose of the study

This program focused on the following topics with the aim to find relevant answers to each of the following questions:

- What is the biologic response to particulate wear debris from THR?
- What is the role of biocompatibility of conventional THR materials and their wear debris in implant loosening?
- Which materials can be safely used in THR prostheses?
- Can wear characteristics of THR bearings be improved?
- Is amorphous diamond biocompatible as THR material?
- Are the wear properties of the THR coated with amorphous diamond suitable for clinically applicable THR?

List of original publications

I Santavirta S, Konttinen YT, Bergroth V, Eskola A, Tallroth K, Lindholm TS. Aggressive granulomatous lesions associated with hip arthroplasty. Immunopathological studies. J Bone Joint Surg (Am) 1990; 72-A:252-8.

II Santavirta S, Xu JW, Hietanen J, Ceponis A, Sorsa T, Konttinen YT. Activation of periprosthetic connective tissue in loosening of total hip replacement. Clin Orthop 1998: (352): 16-24.

III Santavirta S, Konttinen YT, Bergroth V, Grönblad M. Lack of immune response to methylmethacrylate. Acta Orthop Scand 1991; 62: 29-32.

IV Santavirta S, Konttinen YT, Lappalainen R, Anttila A, Goodman SB, Lind M, Smith L, Takagi M, Gómez-Barrena E, Nordsletten L, Xu JW. Materials in total joint replacement. Curr Orthop 1998; 12: 51-7.

V Santavirta S, Takagi M, Gómez-Barrena E, Nevalainen J, Lassus J, Salo J, Konttinen YT. Studies of host response to orthopaedic implants and biomaterials. J Long-term Effects of Medical Implants 1999; 91: 67-76.

VI Santavirta S, Böhler M, Harris WH, Konttinen YT, Lappalainen R, Muratoglu O, Rieker C, Salzer M. Alternative materials to improve total hip replacement tribology. Acta Orthop Scand 2003; 74: 380-8.

VII Nordsletten L, Högåsen AKM, Konttinen YT, Aspenberg P, Aasen A, Santavirta S. Human monocytes are stimulated by particles of hydroxyapatite and silicon carbide, but not by diamond. In vitro studies of new prosthesis coatings. Biomaterials 1996; 17: 1521-27.

VIII Aspenberg P, Anttila A, Konttinen YT, Lappalainen R, Goodman SB, Nordsletten L, Santavirta S. Benign response to particles of diamond and SiC. Bone chamber studies of new joint replacement materials in rabbits. Biomaterials 1996; 17: 807-12.

IX Santavirta S, Lappalainen R, Pekko P, Anttila A, Konttinen YT. The counterface, surface smoothness, and coatings in total joint prostheses. Clin Orthop 1999; (369):92-102.

X Lappalainen R, Selenius M, Anttila A, Konttinen YT, Santavirta S. Reduction of wear in total hip replacement prostheses by amorphous diamond coatings. J Biomed Mater Res 2003; 66: 410-3.

Materials and methods

Modern biological methods were used to study local host response to THR implants. Tribological tests, including simulator studies, were performed to analyze the preclinical performance of THR bearings. Materials and methods are summarized in Table 1, with methodological details in the original publications included in this thesis.

Table 1. Materials and methods used in separate studies I–X

Original publication	Materials	Methods
I	Interface tissue samples obtained from revised THRs	Immunohistochemistry for inflammatory cells
II	Interface tissue samples obtained from revised THRs	Immunohistochemistry for inflammatory cells, Ki-67 staining
III	Fine pulverized methylmethacrylate	Human lymphocyte cultures, 3H-thymidine incorporation, immunocytochemistry
IV	Our previous studies and pertinent literature regarding THR materials	Analysis and review
V	Our previous studies and pertinent literature regarding host response to THR materials	Analysis and review
VI	THR bearings	Tribological techniques
VII	Particulate hydroxyapatite, silicon carbide and amorphous diamond	Human monocyte cultures, immunocytochemistry
VIII	Particulate diamond	Bone-harvesting chamber studies in rabbits
IX	Diamond-coated versus conventional THR bearings	Tribological techniques
X	Diamond-on-diamond THR bearings	Hip-simulator tests

Results

The general results are summarized in Table 2. Detailed results appear in the publications included in this thesis (see list of original publications).

Table 2. Main conclusions of studies I–X THR materials

Original publication	Main results
I	Aggressive periprosthetic granulomatosis is a mainly monocyte-macrophage-dominated adverse foreign-body-type tissue reaction with fibroblastic reactive zones.
II	Around loose THRs, more cell-rich areas and a higher number of activated cells were detectable than around well fixed implants.
III	Methylmethacrylate is immunologically essentially inert.
IV	Cobalt-chromium alloys, methylmethacrylate and polyethylene are still the basic THR materials, showing biologically and tribologically acceptable function.
V	Theoretical and experimental testing is mandatory before introducing new implant materials in a clinical setting.
VI	Metal-on-metal, alumina-on-alumina, and highly cross-linked polyethylene bearings improve tribological properties of THRs.
VII	Diamond particles in a serum-free human monocyte culture are inert, whereas SiC has a stimulatory effect comparable to that of hydroxyapatite.
VIII	SiC and diamond particles were harmless and caused no reduction in bone formation in the bone-harvesting chamber.
IX	Diamond-coated THR bearings offered superior stability and good tribological performance in comparison to any previous THR bearings.
X	After 15,000,000 simulator cycles, diamond-on-diamond THR bearings show no delamination nor measurable wear.

Discussion

Background

The concept of Charnley's original low-friction arthroplasty was based on ultrahigh molecular-weight polyethylene acetabular and metallic femoral components, which were attached to bone with the use of methylmethacrylate. From the beginning, this procedure was clearly more successful than several previous trials that failed because of poor designs and unhappy choice of materials. However, with time it became clear that even in the best series, total hip components gradually tend to become loose, and aseptic loosening still remains the single most important complication of total hip replacement (THR). Wear of articulating and nonarticulating surfaces of the prostheses and the cement and the resulting biological response caused by extensive continuous cyclic loading of the implants contribute to the loosening process. Understanding of the biological- and material-related physical processes occurring in the totally replaced hip form the basis of attempts to improve the currently existing level of THR. The goal of this thesis was to clarify the adverse response to particulate wear debris and learn how this response might be mitigated. Further, the ultimate goal was to produce a nonwearing and highly biocompatible THR prosthesis. The present discussion briefly reviews studies I–X on which this thesis is based.

Aggressive granulomatous type of loosening

In 1989 we focused our interest on the aggressive granulomatous type of loosening, to better understand the process of aseptic THR loosening. At that time, aggressive granulomatosis around cemented THRs had been reported among others by Harris et al. (1976), Jasty et al. (1986) and Tallroth et al. (1989). All these reports confirmed that in some patients aggressive granulomatous lesions may lead to rapid bone lysis around apparently stable cemented arthroplasties in the clear absence of infection and sepsis or of primary mechanical failure (Carlsson et al. 1983). We found that 4.6% of our revision THR arthroplasties showed radiographic evidence of these lesions. At that time the cause of aggressive granulomatous lesions was debated. Today, much knowledge has accumulated but the actual reason why in some THRs this process is initiated and in others not is still to be found. Harris et al. (1976) suggested that cement mantle fragmentation and failure of implant fixation should be blamed, but our results (I) contradict this. Wear of cement caused by micromotion and patient-specific hypersensitivity were at that stage considered hypothetical trigger mechanisms. Bell et al. (1983) and Goldring et al. (1983) had pointed out that the synovial-like biomembrane around the cement was active in production of bone resorption mediators such as prostaglandins and collagenases. Fragmentation of the cement allows deleterious penetration of the wear particles deep into the interface tissue. In order to trace the reason for aggressive granulomatosis, we performed immunopathological studies (I).

Immunohistological evaluation revealed that most cells in the aggressive granulomatous tissue were multinucleated giant cells and C3bi-receptor and nonspecific esterase-positive monocyte macrophages. Aggressive granulomatosis leads to a relative paucity of fibroblast-type cells. This cytological finding suggests a foreign-body-type reaction compatible with the rapidly progressive lytic nature of the lesion (Konttinen et al. 1988). It was uncertain which type of foreign material debris activated the monocyte-macrophages. Charnley (1975, 1979) studied the tissue reaction around cemented prostheses using conventional histology methods and concluded that methylmethacrylate cement was relatively inert, causing little tissue reaction in the well-fixed THR. Among others, Jones and Hungerford (1987) suggested that aggressive aseptic loosening of THR prostheses may be caused by methylmethacrylate cement; this process was called the "cement disease".

One of the problems with aseptic loosening is that on each occasion some part of the original bone stock is destroyed (Amstutz et al. 1982, Wirta et al. 1995). However, we noticed that the use of cementless prostheses did not solve the problem. Clearly, there was a need to improve THR technology to reduce wear and loosening.

THR as a pseudojoint

After surgery, the THR complex is gradually organized into a jointlike space, often referred to as a pseudojoint. Histologically, this pseudojoint shows signs of organization into synovial-like structures with a lining cell layer of fibroblastlike and macrophagelike cells which grow directly on loose connective tissue (Santavirta et al. 1991). This synovial cell layer also produces hyaluronate, which is released into pseudosynovial fluid, resulting in concentrations far exceeding those of peripheral blood and of the same concentrations as observed in synovial joints (Saari et al. 1993). Local proliferation of fibroblasts and vascular endothelial cells in periprosthetic tissues may reflect healing and active tissue remodeling in the pseudocapsule of the artificial joint. Activation of the same cells in the interface tissue between implant or implant-cement-complex and bone may be caused by foreign bodies or cyclic loading or both (Jiranek et al. 1993, Kim et al. 1993, Goodman 1994). Cytofluorographic studies have implied that cells synthesizing DNA are significantly more numerous in such tissues (Santavirta et al. 1990). To assess the eventual activation and proliferation of local cells in periprosthetic tissues in loose THRs, samples of such tissue were stained with specific antibodies directed against a cell proliferation marker known as Ki-67 antigen (Brown and Gatter 1990) (II). The fibrous areas and, in particular, the cell-rich vascular areas of the interface tissue (between implant and bone) and the pseudocapsule around aseptically loosened implants contained higher numbers of proliferating cells than did the tissues around well-fixed implants. In addition, the pseudosynovial lining occasionally contained some Ki-67-positive proliferating cells. It became clear that reactive (interface tissues) and adaptive (pseudojoint capsule) tissue changes occurr in loosening THRs which result from proliferation of local fibroblastlike cells. These activated mesenchymal tissues, however, showed no malignant changes.

Cement disease?

Methylmethacrylate is one of the most common materials implanted in man. Earlier histologic studies of human retrieval samples (Charnley 1979, Linder and Hanson 1983) and of animal-experiments (Draenert 1981) have demonstrated that long-lasting close contact between cement and bone may be achieved without signs of tissue irritation. However, at that stage, research regarding immunocompatibility of methylmethacrylate cement was based on indirect evidence. We therefore analyzed whether or not finely pulverized methylmethacrylate in human peripheral blood lymphocyte cultures was immunologically inert (III). Phytohemagglutin (PHA) lectin, purified protein derivate of tuberculin (PPD) antigen, or culture medium alone served as positive and negative controls on studied days 0, 1, 3 and 5. Major histocompatibility complex locus II antigen (MHC locus II antigen;Ia) and interleukin-2 receptor (IL-2R);Tac) expression were analyzed by the ABC method, and lymphocyte DNA synthesis by 3H-thymidine incorporation and beta-scintillation counting. The results suggested that although methylmethacrylate is essentially an immunogically inert implant material, it seems, however, to induce inflammatory mononuclear cell migration and adhesions, leading to a slightly nonspecific lymphocyte and macrophage reaction (Wimhurts et al. 2001). The nonimmunological type of monocyte activation which we detected may also be responsible for the cellular profile observed in periprosthetic tissue in THR loosening (Brooks et al. 2000).

Cemented versus cementless hip arthroplasty

Because of increased numbers of loosened cemented arthroplasties, it became popular to perform primary and revision THR arthroplasties without the use of methymethacrylate cement (VI). Some surgeons still considered that the adverse effects of mechanical loosening to be overemphasized, and for many years it was thought that the polyethylene and methylmethacrylate wear debris was of benign nature (Wroblewski 1979, Editorial, Lancet 1990). In Finland, the cementless THR became the common clinical choice in the 1980s, and initially the clinical results seemed to be good. After a few years some of these prostheses failed because of poor design.. For example the threaded cups were later replaced by press-fit components, but in some designs the locking mechanisms between metallic component and polyethylene liner were insufficient. Moreover, in small cups the thin polyethylene liner fractured easily. In cementless titanium based THRs also articulating titanium-based balls were used in the early period. These caused excessive metallic and polyethylene wear, which accelerated the loosening process (Agins et al. 1988). The elasticity modules of different metals and bone were also quite different. According to the basic principles of performance of materials, cyclic loading of a such a combination (bone-metal) would be likely to cause either deformation or loosening at some part of the interface. Today, we know that some of the cementless stems have been very successful (Lord et al. 1988), but the different cementless acetabular components have usually had shorter survival times than have their cemented counterparts, a fact shown in several Scandinavian implant register studies. It also became clear that better preclinical studies were necessary before introducing any new THR designs into clinical use.

In order to improve cementless fixation, hydroxyapatite coating of the implant surface (often titanium) was considered the method to improve bonding between implant and bone. Hydroxyapatite is very biocompatible, but easily becomes delaminated from the implant and then pulverized into small-particle wear debris (Santavirta et al. 1991). Experimental and developmental work has now improved the quality of hydroxyapatite coatings, and the newer hydroxyapatite-coated THRs probably produce a solid and long-lasting bonding to bone.

Lord et al. (1988) and Santavirta et al. (1990) reported adverse bone reactions leading to loosening in cementless THRs meaning that not only methylmethacrylate could be blamed for granulomatous lesions or common aseptic loosening. In clinical interface and pseudocapsular samples, CD11b- and CD68-positive cells dominate the cellular reaction mainly caused by polyethylene-wear debris (Santavirta et al. 1993A). In human lymphocyte cultures, polyethylene debris behaves very much as does methylmethacrylate; the material seems to be immunologically biocompatible but causes a foreign-body type reaction which may be more severe than from methylmethacrylate because the particles are frequently of submicron size and the shape may be very irregular.

Matrix metalloproteinases in THR loosening

Histological evidence exists that a monocyte/macrophage reaction against implant wear particles (methylmethacrylate, polyethylene, metallic, ceramic) may precede the instability and sometimes may be the primary cause of loosening (Willert et al. 1984, Pazzaglia et al. 1988, Pazzaglia 1990). Macrophages have been shown to produce interstitial collagenase identical to fibroblast collagenase (Konttinen et al. 1991). This suggests that the local phagocytic and secretory macrophages try to respond to the stimulus initiating the adverse tissue reactions complicating both cemented and cementless THR arthroplasty (Santavirta et al. 1993B). It appeares likely that interstitial collagenase contributes to the sometimes rapid growth of reactive infiltrative tissue connected with loosening of the THR prosthesis. Blood and healthy tissues contain tissue inhibitors of matrix metalloproteinases (TIMP). The aggressive periprosthetic granuloma formation occasionally occurring is apparently the result of an imbalance between collagenase- and TIMP-production controlling mechanisms. Particle generation from wear of the prosthesis also plays a significant role as an inducer of nitric oxide synthase and cyclooxygenase 2 (Hukkanen et al. 1998, Suh et al. 2002).

We hypothesized that aseptic loosening of THR implants is usually a result of cyclic mechanical loading combined with biological responses in which proteolytic enzymes play an important role (Takagi 1996). Because extracellular matrix degradation in vivo occurs in the extracellular space at neutral pH, the extracellular proteinases, which are active at physiological pH, are important in the cascade of connective-tissue degradation both in normal and in pathological tissues. Type IV collagens are digested by gelatinase/type-IV collagenases (MMP-2/72kDa and MMP-9/92 kDa) as shown by us (Takagi et al. 1994). Zymographic and densitometric analyses revealed elevated production of MMP-2 and induction of MMP-9 in tissue extracts from both the interface tissues and the pseudocapsular tissues around loose THRs. The level of MMP-9 was higher in the former than in the latter. The pseudocapsular tissue reactions may contribute to prosthetic loosening via the production and release of matrix metalloproteinases into the synovial fluid. The pumping mechanism created by cyclic loading leads the fluid to the interphase space between bone and implant/cement complex, and through cracks in the cement, the fluid may penetrate even further.

During our studies, techniques for research on matrix metalloproteinase activity in the context of THR loosening developed rapidly. It became clear that an excess of matrix metalloproteinases, including MMP1, MMP2, MMP9, MT1 MMP, and possibly MMP13, plays an important role in the periprosthetic weakening, contributing to aseptic loosening and osteolysis around loose THRs (Takagi et al. 1998). This understanding is essential if attempts are made biologically or chemically to reduce local periprosthetic matrix metalloproteinase activity.

Materials in total hip replacement

The optimal materials for THR have been debated. Materials chosen must be biocompatible (both the material itself and any breakdown products), strong, resistant to fatigue, wear, and corrosion, easily accessible and reasonably priced (IV,V). For many years, the material chosen by John Charnley in the early 1960s (namely stainless steel, polyethylene, and methylmethacrylate) remained the ”gold standard” for comparison (Charnley 1972). Later, metallic alloys of cobalt-chrome or titanium were used. In general, these alloys are stronger and more corrosion- and wear-resistant than stainless steel (Wright and Goodman 1995). Such theoretical benefits have to be documented in clinical outcome. Papers IV and V review our and other researchers’ experience regarding currently used THR materials.

Stainless steel

Improved stainless steels are still used in current THR designs as the major load-bearing joint (Cook 1995). These steel materials are iron-based alloys containing appreciable amounts of chromium, nickel, and molybdenum. Stainless steel is usually annealed, cold-worked, or cold-forged to improve alloy strength. A potential problem is the relatively high modulus of elasticity of stainless steel, which is about 200 GPa. This value is about 10 times higher than for bone. Methylmethacrylate mitigates the stress-shielding effects of stainless steel, which is still quite a suitable THR material. In body, stainless steel as all metallic THR materials are subjects to different types of corrosion. For example, taper fretting and corrosion may be found in revised modular hip prostheses (Goldberg et al. 2002).

Cobalt-chromium alloys

Cobalt-chromium alloys are stronger and more corrosion-resistant than stainless steel. These alloys are usually composed of 30–60% cobalt, 20–30% chromium, and 7–10% molybdenum, and various amounts of nickel (Gibbon 1982, Cook 1995). Heat and pressure improve their strength. Their modulus of elasticity is slightly higher than that for stainless steel (250 GPa). Cement fixation modulates the different elasticity modules of the bone and the implant. Prosthetic fractures are rare. Stress shielding of the periprosthetic bone is also a potential problem, especially when the material is used for cementless femoral components. Currently cobalt-chromium alloy-based metal-on-metal total hip prostheses have again become popular (Rieker and Köttig 2002). Although cobalt-chromium alloys are hard and tough, there is constant metal release from prosthetic articulations based on these metals (Saikko et al. 1998). In fact.dissemination of such metal particles to the liver and spleen has been reported even in the case of well-functioning prostheses (Urban et al. 200). Recent research shows that cobalt ions influence the proliferation and function of human osteoblast-like cells (Goodman et al. 1995, Anissian et al. 2002). Cobalt-chromium alloy-based metal-on-metal THR designs were popular in the early phase of modern THR surgery. In the 1990s such designs have been improved. The early clinical experience are generally good (VI).

Titanium alloys

Titanium alloys have become popular in THR components designed for cementless fixation. Ti-6Al-4V is a common alloy composed of approximately 90% titanium and almost equal parts of aluminum and vanadium. Titanium alloy is strong and corrosion-resistant, and has a modulus of elasticity (110 GPa) about half of that of stainless steel and cobalt-chromium. Theoretically, stress shielding should be less with a material having an elasticity modulus closer to that of the bone. The wear characteristics of titanium can be improved by surface treatment processes such as ion implantation, but such a surface tends to wear out very soon, and is not suitable as an articulating component. The titanium femoral stem should be paired with head of cobalt-chromium or ceramic. Some newer titanium alloys such as Ti-13Zr-13Nb are even stronger than conventional titanium alloys and have a lower modulus of elasticity. Evidence exists that titanium may be less suitable for cemented fixation. For such use, it should probably be at least highly polished and preferably coated with a ceramic surface. There is some evidence that commercially pure titanium and titanium-based alloys may favor bone apposition and ingrowth to a greater degree, than cobalt-chromium alloys (Johansson 1991). On the other hand, titanium particles have a stimulatory effect on resident macrophages (Soloviev et al. 2002). The future of THR technology is to a great extent dependent on correct choice of metallic materials (Wright and Goodman 1995).

Polyethylene

The THR debate in the 1990s has been focused on polyethylene wear, because increasing numbers of otherwise successful total joints have failed. The material of choice is ultra-high molecular-weight polyethylene (UHMWPE). The industrial production of basic UHMWPE powder involves very few manufacturers. The molding and irradiation used to produce crosslinked UHMWPE vary. In the molding process, UHMWPE powder is heated above its melting point. Any time UHMWPE reaches an elevated temperature, the potential arises of alteration in its physical properties.

Oxidation of the polyethylene has been reported in retrieved implants as well as in new components after gamma sterilization (Li and Burstein 1994). The shelf-life of UHMWPE acetabular components has an important effect on their later wear properties (Barrena et al. 1996). Average wear in the cup is still between 0.1 and 0.2 mm/year. The early wear of the new highly crosslinked UHMWPE components is smaller (VI). The wear of polyethylene has been linked with the loosening processes (III, V). The presence of particulate polyethylene is known to be sufficient to cause an aggressive periprosthetic tissue response and in the case of an unstable interface prevents the formation of new bone (Bechtold et al. 2002). Any means of reducing or totally avoiding wear for polyethylene is very important. This can be achieved by developing better polyethylenes, by tribologically better femoral heads or better prostheses, for example of metal-on-metal and alumina-on-alumina types. Each design has its advantages but also drawbacks. A prosthetic system showing little wear easily becomes too rigid or shows inferior shock-absorbing properties.

Ceramics

Ceramics in THR are classified into materials that are bioinert (alumina and zirconia) or bioactive (hydroxyapatite and glass ceramics). The bioinert ceramics are suitable as femoral head material and hydroxyapatite as a coating material in cementless prostheses (Wang et al. 1994). The wear products are abrasive and easily destroy the bearing surfaces, resulting in excessive wear. Recent work has shown that alumina-on-alumina bearings are a good alternative, and also improve the tribological properties of the THR (VI). Ceramic coating of the bearing surfaces is possible (such as with amorphous diamond). In the case of delamination of such surfaces, the particles created may, however, irritate the periprosthetic tissues.

Coatings

In total hip replacements, the bulk properties of materials such as elasticity and hardness are important (Lappalainen and Santavirta 2004). However, the material interacts with the body mainly at the surfaces and wear and corrosion occur here. Therefore, the control of surface properties by using different kind of treatments or coatings can enhance the properties of THRs significantly. Most studied surface treatments include ion implantation and methods to control surface topography such as grid or sand blasting or plasma treatments. Titanium oxide, nitride, zirconium oxide, pyrolactic carbon and diamond like carbon coatings have given the most promising results.

Diamond

In human monocyte-culture studies, diamond particles appear quite inert (VII). In order to further study the biocompatibility of diamond in bone, we applied the bone-harvest chamber method in rabbits (Albrektsson et al. 1984, Goodman 1994) (VIII). We found that methylmethacrylate, polyethylene and cobalt-chromium caused a reduction of bone formation, whereas, neither diamond nor SiC particles caused any such reduction in bone formation. It appeared that particles of diamond and of SiC were comparably harmless when inserted into bone. SiC whiskers can be used to improve adhesion between coating and substrate and guarantee extreme adhesion even in the case of the high internal stresses characteristic for amorphous diamond coatings with a high sp3 fraction of diamond bonding (Anttila et al. 1995).

Testing of materials

Studies of the host response to orthopedic implants and biomaterials have become very important in preventing clinical failures (V). To date, many different materials have been tried to reduce wear and generation of macrophage-irritating submicron-size particles or to provide more biocompatible materials. However, trials to improve the methylmethacrylate cement or to invent better polyethylene have often failed. Diamond coating of the metallic components seems promising: less wear occurs and diamond is very compatible both in bulk and in small particulate form. Extensive biological and mechanical testing is, however, necessary each time new materials and designs are planned (Goodman et al. 1998).

Regarding in vitro tribological studies of total hip bearings, a variety of factors influence the action of wear mechanisms (Wimmer et al. 2001). For example, the effects of lubricants on the friction of total hip prostheses is very important, and nonbiological lubricants should not be relied upon in tests of new designs of total hip prosthesis bearing surfaces (Scholes et al. 2000). Diluted bovine serum is currently universally accepted as the test lubricant.

Since wear debris probably causes many of the harmful processes involved in prosthesis loosening, there appears to be a definite need for a prosthetic material that has more optimal wear characteristics than the traditional materials. Currently we are working on the development of a THR prosthesis with amorphous diamond coating deposited using a novel pulsed plasma acceleration method (Anttila et al. 1997).

Biocompatibility of diamond

In the case that diamond would be applied as a THR coating material, it had to be tested for biocompatibility issues. Huiskes (1993) and Harris (1994) have warned for failed innovations and have pointed out the need for profound laboratory testing of new materials. Material scientists have discussed the need to strengthen the diamond coating with SiC whiskers to improve adhesion. We tested the biocompatiblity of these materials in small-particle form in human monocyte cultures (VII). In macrophage-particle interaction, the size, composition, and surface area are of importance (Shanbhag et al. 1994). Mainly, particle sizes were for each material from 2 to 5 microns. All particles were phagocytozed, and monocyte morphology changed, except after the ingestion of diamond. Interleukin-1beta production was on average 30-fold and 38-fold in cultures exposed to HA or SiC, compared to controls and diamond cultures. In some cultures, methylmethacrylate was also included, and its stimulatory effect on interleukin-1beta production was in the same range as with HA or SiC. These studies showed that diamond particles in a serum-free monocyte culture were inert, whereas HA and SiC had a stimulatory effect comparable to that of methylmethacrylate. Because of its excellent tribological and biocompatible properties, further studies of diamond coatings are warranted.

The bone-harvest chamber in rabbits has proven to be a suitable method for testing the biocompatibility of orthopedic implant materials (Albrektsson et al. 1984). Studies on cobalt-chromium alloys, polyethylene, hydroxyapatite, and methylmethacrylate have appeared, and their results serve as controls for future tests (Goodman 1994, Goodman et al. 1995). We dispersed particles of diamond and SiC in hyaluron and introduced this to a canal traversing the implant (VIII). Tissue that entered this canal during the following 3 weeks was then harvested. In previous studies, each of these THR materials induced an inflammatory reaction and reduced new bone formation. In the present study, neither diamond nor SiC had any adverse effect on bone formation. It appears that particles of diamond and SiC are comparatively harmless in bone.

Deposition and physical properties of diamond coating

Tetrahedal amorphous carbon/diamond coatings have several advantageous properties comparable to those of natural diamond (Pekko 2000). Especially high hardness, modulus of elasticity, wear resistance, chemical inertness, transparency, biocompatibility, low barrier to electron emission and low friction against several materials. On the other hand, the coatings have high internal stresses, which presents high demands on the adhesion to the substrate. Similar to natural diamond, the structure of such coatings is metastable, but in inert atmospheres they remain stable in temperatures up to 1000 °C and in the case of oxygen invironment up to 550 °C.

The filtered cathodic vacuum arc process has proven to be a reliable technique that can produce extremely high quality coatings with good bonding (Hakovirta et al. 1999). This technique is relatively inexpensive, relatively simple and well applicable for industrial use. Research has shown that such coatings have extremely good abrasive wear resistance (Lappalainen and Pekko 1997).

Tribological considerations

Proper counterface material combinations, surface finish, and tolerances of contact surfaces are important issues in minimizing friction, wear, and corrosion of THR prostheses (Saikko et al. 1993). The new highly crosslinked polyethylenes, alumina-on-alumina and metal-on-metal bearings are well-functioning solutions available to improve tribological properties (VI). We studied the potential of novel amorphous diamond coatings (Anttila et al. 1997, Lappalainen et al. 1998), to solve some current problems in THR prostheses by using tribological tests with a hip-joint simulator and pin-on-disk testers (McKellop 1998). According to our hypothesis, a diamond coating can be used on any metallic THR material, including stainless steel, in the bearings. A diamond-coated femoral head can be paired with a polyethylene acetabular cup or a metallic cup, preferably also coated with a diamond layer.

In this study, “amorphous diamond coating” refers to a hydrogen-free tetrahedral amorphous carbon film prepared with physical vapor deposition methods. Such films are extremely hard, show a low coefficient of friction and have no open corrosion paths to the substrate. Moreover, since the deposition temperature is relatively low, these coatings do not suffer from thermally induced stress. Based on our tests, the wear of amorphous diamond was negligible, and was 10^4 to 10^5 times lower than in conventional THR articulations (IX, X). The coefficient of friction of the diamond-coated artificial hip joint was 0.03 to 0.06 when tested in a saline solution with loads from 200 to 1000 kg for as many as 2 million cycles. The friction remained stable throughout the tests. Methylmethacrylate (bone cement) is a typical source of third-body wear particles in cemented THRs. The wear tests showed that bone cement, containing hard ceramic particles of hydroxyapatite or zirconia, severely scratched cobalt-chromium alloy samples. These scratches accelerated the wear of softer counterpart materials, such as polyethylene, whereas diamond-coated samples remained unchanged. High quality amorphous diamond coatings offer superior stability (minimal wear-debris release in surrounding tissues) and good biomechanical performances, leading to longevity of the THR.

In order to plan a THR implant with theoretically minimal wear, we decided to test 28-mm and 35-mm femoral heads made of stainless steel (AISI3 16L) paired with a comparable acetabular cup and polished mechanically to give a typical surface roughness of 5–10 nm. An amorphous diamond coating was deposited on the bearing surfaces by the technique described by Anttila et al. (1997). After deposition, clearance between ball and cup was about 100 microns. The wear-rate measured in a commercial 6-channel hip-simulator for 15 million walking cycles (comparable to 15 clinical THR years; Schmalzried et al. 1997) with serum lubrication was negligible, i.e. 1,000,000-fold lower than in conventional metal-on-polyethylene or metal-on-metal THR pairs (McKellop 1998). The coatings remained smooth during the test and did not delaminate. It can thus be concluded that high-quality amorphous diamond coatings lead to markedly reduced wear in hip simulators. In the various tests we have performed, diamond coating produced according to Anttila et al. (1997) has not delaminated even when forces exceeding by far the ones acting in clinical THRs were applied. In diamond-on-diamond THR design, particulate diamond addition in the lubricant has not caused damage on the bearing surfaces.

Conclusions

- THR loosening is a result of adverse biological reactions mainly initiated by implant wear products, in combination with mechanical cyclic loading (I, II).

- Conventional THR materials are usually very biocompatible in bulk form but their small particulate wear products cause foreign-body type cellular reactions (III, IV).

- In the THR, these wear-products irritate resident macrophages both in the interface and in pseudocapsular tissues, leading to excess production of several matrix metalloproteins, which are some of the important enzymes weakening the THR anchorage tissues (V).

- THR materials should show good biocompatibility characteristics both in bulk and in small particulate form, should be resistant to wear and corrosion, and should have reasonable elastical properties (to avoid stress-shielding) (V, VI) .

- Amorphous diamond coating seems to be very biocompatible, and practically nonwearing, which is necessary for increased longevity of the THR (VII, VIII, IX, X).

Acknowledgements

This study was carried out as part of the Finnish Academy sponsored center of excellency program for tissue engineering and biomaterials research. Several universities and research centers participated in our biomaterial-study net-work: University of Helsinki, University of Kuopio, University of Lund, University of Oslo, University of Vienna, University of Zaragoza, University of Stanford and Massachusetts General Hospital. I wish to express my deepest gratitude to everyone who has contributed to my work and supported the studies included in this thesis.

Especially, I wish to address my warm thanks to Professor Reijo Lappalainen, University of Kuopio and Professor Asko Anttila, University of Helsinki (emeritus), who both are famous for important innovations in diamond-coating technology. Professor Yrjö T. Konttinen, University of Helsinki, has been a close research associate in chemical and biological studies. Associate Professor William A. Jiranek, Virginia Commonwealth University, and Docent Jukka Jurvelin, University of Kuopio have reviewed the thesis and they both gave valuable comments, which were helpful in completing the manuscript. Several co-workers, many of them close friends have helped me with the separate studies, on which this thesis is based on. I want to express my best gratitude to you all.

The research included in my thesis was economically supported by the Finnish Academy, TEKES, Helsinki University Central Hospital, Research ORTON, the Juselius Foundation, and Finska Läkaresällskapet. I am most grateful to each of these institutions.

References

Agins HJ, Alcock NW, Bansal M, Salvati EA, Wilson PDJr, Pellicci PM, Bullough PG. Metallic wear in failed titanium-alloy total hip replacements. J Bone Joint Surg 1988; 70-A: 347-56.

Albrektsson T, Jacobsson M, Kalebo P. The harvest chamber—a newly developed implant for analysis of bone remodelling in situ. In: Biomaterials and biomechanics (Eds. Ducheyne P, Van der Perre G, El Ubert A). Amsterdam: Elsevier Science 1984, pp: 283-8

Amstutz HC, Ma SM, Jinnah RH, Mai L. Revision of aseptic loose total hip arthroplasties. Clin Orthop 1982; (170): 21-33.

Anissian L, Stark A, Dahlstrand H, Granberg B, Good V, Bucht E. Cobalt ions influence proliferation and function of human osteoblast-like cells. Acta Orthop Scand 2002; 73: 369-74.

Anttila A, Salo J, Lappalainen R. High adhesion of diamond like films achieved by pulsed arc discharge method. Mater Lett 1995; 24: 153-6.

Anttila A, Lappalainen R, Tiainen VM, Hakovirta M. Superior attachment of high-quality hydrogen-free amorphous diamond films to solid materials. Adv Mater 1997; 9: 1161-4.

Bechtold JE, Kubic V, Soballe K. Bone ingrowth in the presence of particulate polyethylene. J Bone Joint Surg (Br) 2002; 84-B: 915-9.

Bell RS, Haéri GB, Goodman SB, Fornasier VL. Case report 246: osteolysis of the ilium associated with a loose acetabular cup following total hip arthroplasty, secondary to foreign body reaction to polyethylene and methyl methacrylate. Skeletal Radiol 1983; 10: 201-4.

Brooks RA, Sharpe JR, Wimhurst JA, Myer BJ, Dawes EN, Rushton N. The effects of the concentration of high-density polyethylene particles on the bone-implant interface. J Bone Joint Surg (Br) 2000; 82-B: 595-600.

Brown DC, Gatter KC. Monoclonal antibody Ki-67: Its use on histopathology. Histopathology 1990; 17: 489-503.

Brown SR, Davies WA, DeHeer DH, Swanson AB. Long-term survival of McKee-Farrar total hip prostheses. Clin Orthop 2002; (402):157-163.

Callaghan JC, Albright JC, Goetz DD, Olejniczak JP, Johnston RC. Charnley total hip arthroplasty with cement: Minimum twenty-five year follow-up. J Bone Joint Surg (Am) 2000; 82-A: 487-97.

Carlsson ÅS, Gentz C-F, Linder L. Localized bone resorption in the femur in mechanical failure of cemented total hip arthroplasties. Acta Orthop Scand 1983; 54: 396-402.

Charnley J. Proceedings: The histology of loosening between acrylic cement and bone. J Bone Joint Surg (Br) 1975; 57-B: 245.

Charnley J. The long-term results of low friction arthroplasty of the hip performed as a primary intervention. J Bone Joint Surg (Br) 1972: 54-B: 61-76.

Charnley J. Low friction arthroplasty of the hip. Theory and practice. Springer, Berlin 1979, pp: 25-40.

Cook SD. Materials consideration in total joint replacement. In: Hip and knee reconstruction (Eds. Callaghan JJ, Dennis DA, Paprowsky WG, Rosenberg AG). Orthopaedic knowledge update. Rosemont, Il: American Academy of Orthopaedic Surgeons 1995, pp: 27-33.

Draenert K. The John Charnley Award Paper. Histomorphology of the bone cement interface: remodelling of the cortex and revascularization of the medullary canal in animal experiments. Hip 1981: 71-110

Dumbleton JH, Manley MT, Edidin AA. A literature review of the association between wear rate and osteolysis in total hip arthroplasty. J Arthroplasty 2002; 17: 649-59.

Editorial: Granulomatous reaction in total hip arthroplasty. Lancet 1990; 335: 203.

Gibbons DF. Materials for orthopaedic joint prostheses. In: Biocompatibility of orthopaedic implants (Ed. Williams DF). Vol. I. Boca Raton, FL: CRC Press 1982, pp: 112-3.

Goldberg JR, Gilbert JL, Jacobs JJ, Bauer TW, Paprosky W, Leurgans S. A multicenter retrieval study of the taper interfaces of modular hip prostheses. Clin Orthop 2002; (401): 149-61.

Goldring SR, Schiller AL, Roelke M, Rourke CM, O´Neill DA, Harris WH. The synovial-like membrane in the bone-cement interface in loose total joint replacements and its proposed role in bone lysis. J Bone Joint Surg (Am) 1983; 65-A: 575-84.

Gomez-Barrena E, Chang JD, Li S. The role of polyethylene properties in osteolysis after total hip replacement. In: Instructional course lectures 45 (Ed. Pritchard DJ): Rosemont, IL: American Academy of Orthopaedic Surgeons 1996 pp: 187-97.

Goodman SB, Davidsson JA, Fornasier VL. Histological reaction to titanium alloy and hydroxyapatite particles in the rabbit tibia. Biomaterials 1993; 14: 723-8.

Goodman SB. The effects of micromotion and particulate materials in tissue differentiation. Bone chamber studies in rabbits. Acta Orthop Scand 1994; Suppl 258: 1-43.

Goodman SB, Aspenberg P, Song Y, Doshi A, Regula D, Lidgren L. The effects of particulate cobalt chrome alloy and high density polyethylene on tissue ingrowth into the bone harvest chamber in rabbits. J Bone Joint Surg (Am) 1995; 77-A: 1025-35.

Goodman SB, Lind M, Song Y. Smith RL. In vitro, in vivo and tissue retrieval studies on particulate debris. Clin Orthop 1998; (352): 25-34.

Hakovirta M, Tiainen VM, Pekko P. Techniques for filtering graphite macroparticles in the cathodic vacuum arc deposition of tetrahedal amorphous carbon films. Diamond and Related Materials 1999; 8: 1183-92.

Harris WH, Schiller AL, Scholler JM, Freiberg RA, Scott R. Extensive localized bone resorption in the femur following total hip replacement. J Bone Joint Surg (Am) 1976; 58-A: 612-8.

Harris WH. Osteolysis and particle disease in hip replacement—a review. Acta Orthop Scand 1994; 65: 113-23.

Havelin HI, Engsaeter IB, Espehaug B, Furnes O, Lie SA, Vollseth SE. The Norwegian arthroplasty register: 11 years and 73,000 arthroplasties. Acta Orthop Scand 2000; 71: 337-53.

Herberts P, Malchau H. How outcome studies have changed total hip arthroplasty practices in Sweden. Clin Orthop 1997; (344): 44-60.

Huiskes R. Failed innovation in total hip replacement diagnosis and proposals fo a cure. Acta Orthop Scand 1993; 64: 699-717.

Hukkanen M, Corbett SA, Platt LAM, Konttinen YT, Santavirta S, Highes SPF, Polak JM: Nitric oxide in the local host reaction to total hip replacement. Clin Orthop 1998; (352): 53-65.

Jiranek WA, Machado M, Jasty M, Jevsevar D, Wolf HJ, Goldring SR, Harris WH. Production of cytokines around loosened cemented acetabular components. J Bone Joint Surg (Am) 1993; 75-A: 863-79.

Johansson CB. On tissue reactions to metal implants. PhD thesis, Gothenburg, Sweden 1991.

Jones LC, Hunerford DS. Cement disease. Clin Orthop 1987; (225): 192-206.

Kim KJ, Rubash HE, Wilson SC, Dantonio JC, McLain EJA. A histologic and biochemical comparison of the interface tissues in cementless and cemented hip prostheses. Clin Orthop 1993; (287): 142-52.

Konttinen YT, Saari H, Santavirta S, Antti-Poika A, Sorsa T, Nykänen P, Kemppinen P. Synovial fibroblasts (a review). Scand J Rheumatol 1988; Suppl 76: 95-103.

Konttinen YT, Lindy O, Suomalainen K, Saari H, Vauhkonen M, Lauhio A, Santavirta S. Substrate specificity and activation mechanisms of collagenase from human rheumatoid synovium. Matrix 1991; 11: 395-402.

Lappalainen R, Pekko P. Tetrahedal amorphous carbon (ta-C) coatings for processing tools to reduce comtamination in the analysis of trace elements. Diamond and Related Materials 1997; 6: 1207-9.

Lappalainen R, Anttila A, Heinonen H. Diamond coated total hip replacements. Clin Orthop 1998; 352: 118-27.

Lappalainen R, Santavirta S. Potential of coatings in total hip replacement. Clin Orthop 2004; In press

Li S, Burstein AH. Ultra high molecular weight polyethylene. The material and its use in total hip joint implants. J Bone Joint Surg (Am) 1994; 76-A: 1080-90.

Linder L, Hansson HA. Ultrastructural aspects of the interface between bone and cement in man. Report of three cases. J Bone Joint Surg (Br) 1983; 65-B: 646-9.

Lord G, Marotte JH, Blanchard JP. Cementless madreporic and polasized total hip prosthesis: a ten-year review of 2688 cases. French J Orthop Surg 1988; 2: 82-92.

McKellop H. Assessment of wear of materials for artificial joints. In: The adult hip (Eds. Callaghan J, Rosenberg A, Rubash H). New York. Lippingott-Raven 1998; pp: 231-46.

Muratoglu OK, Bragdon CR, O´Connor DO, Jasty M, Harris WH, Gul R, McGarry F. Unified wear model for highly crosslinked ultra-high molecular weight polyethylene (UHMWPE). Biomaterials 1999; 20: 1463-70.

Pazzaglia UE, Pringle JA. The role of macrophages and giant cells in loosening of total hip replacement. Arch orthop Trauma Surg 1988; 107: 20-6.

Pazzaglia UE. Pathology of bone cement interface in loosening of total hip replacement. Arch Orthop Trauma Surg 1990; 109: 83-8.

Pekko P. Experimental studies of tetrahedal amorphous carbon coatings. Acta Polytechnica Scandinavica; Applied Physics Series 2000; no 223, pp 1-30,

Puolakka TJ, Pajamäki KJ, Pulkkinen PO, Nevalainen JK. Poor survival of cementless Biomet total hips: A report on 1.047 hips from the Finnish Arthroplasty Register. Acta Orthop Scand 1999; 70: 425-9.

Rieker C, Köttig P. *In vivo* tribological performance of 231 metal-on-metal hip articulations. Hip International 2002; 12: 73-6.

Saari H, Santavirta S, Nordström D, Paavolainen P, Konttinen YT. Hyaluronate in total hip replacement. J Rheumatol 1993; 20: 87-90.

Saikko V, Paavolainen P, Slätis P. Wear of the polyethylene acetabular cup. Metallic and ceramic heads compared in a hip simulator. Acta Orthop Scand 1993; 64: 391-402.

Saikko V, Nevalainen J, Revitzer H, Ylinen P. Metal release from total hip articulations in vitro. Acta Orthop Scand 1998; 69: 449-54.

Santavirta S, Konttinen YT, Bergroth V, Eskola A, Tallroth K, Lindholm TS. Aggressive granulomatous lesions associated with hip arthroplasty. Immunopathological studies. J Bone Joint Surg (Am) 1990; 72-A: 252-8.

Santavirta S, Konttinen YT, Hoikka V, Eskola A. Immunopathological response to loose cementless acetabular components. J Bone Joint Surg (Br) 1991; 73-B: 38-42.

Santavirta S, Gristina A, Konttinen YT. Cemented versus cementless THR. Prosthetic biocompatibility. Acta Orthop Scand 1992; 53: 225-32.

Santavirta S, Nordström D, Ylinen P, Konttinen YT. Biocompatibility of polyethylene and host response to loosening of cementless total hip replacement. Clin Orthop 1993A; (295): 100-10.

Santavirta S, Sorsa T, Konttinen YT, Saari H, Eskola A, Eisen AZ. Role of mesenchymal collagenase in the loosening of total hip prosthesis. Clin Orthop 1993B; (290): 206-15.

Santavirta S. Editorial comment. Clin Orthop 1998; (352): 2-3.

Schmalzried TP, Peters PC, Maurer BT. Long-duration metal-on-metal total hip arthroplasty with low wear of the articulating surfaces. J Arthroplasty 1996; 11: 322-31.

Scholes SC, Unsworth A, Hall RM, Scott R. The effects of material combination and lubricant of the friction of total hip prostheses. Wear 2000; 241: 209-13.

Soloviev A, Schwarz EM, Kuprash DV, Nedospasov SA, Puzas JE, Rosier RN, O´Keefe RJ. The role of p105 protein in NkkappaB activation in ANA-1 murine macrophages following stimulation with titanium particles. J Orthop Res 2002; 20: 714-22.

Suh KT, Chang JW, Jung JS. The role of inducible nitric oxide synthase in aseptic loosening after total hip arthroplasty. J Bone Joint Surg (Br) 2002; 84-B: 753-7.

Takagi M, Konttinen YT, Lindy O, Sorsa T, Kurvinen H, Suda A, Santavirta S. Gelatinase/Type IV collagenase in the loosening of THR endoprostheses. Clin Orthop 1994; (306):136-44.

Takagi M. Neutral proteinases and their inhibitors in the loosening of total hip prostheses. PhD thesis, Helsinki 1996

Takagi M, Santavirta S, Ida H, Ishii M, Konttinen YT. Matrix metalloproteinases and tissue inhibitors of metalloproteinases in loose artificial hip joints. Clin Orthop 1998; (352): 35-45.

Tallroth K, Eskola A, Santavirta S, Konttinen YT, Lindholm TS. Aggressive granulomatous lesions in hip arthroplasty. J Bone Joint Surg (Br) 1989; 71-B: 571-5.

Walker P. Innovation in total hip replacement– When is a new better? Clin Orthop 2000; (381): 9-25.

Wimhurst JA, Brooks RA, Rushton N. Inflammatory responses of human promary macrophages to particulate bone cement. J Bone Joint Surg (Br) 2001; 83-B: 278-82.

Wimmer MA, Loos J, Nassutt R, Heitkemper M, Fischer A. The acting mechanisms on metal-on-metal hip joint bearings. Wear 2001; 250: 129-39.

Wirta J, Eskola A, Santavirta N, Hoikka V, Lindholm TS, Santavirta S. Outcome of multiple THR revisions. J Orthop Rheumatol 1995; 8: 23-5.

Wright TM, Goodman SB (eds): Implant wear. The future of total joint replacement. Rosemont, IL: American Academy of Orthopaedic Surgeons 1995: 1-109.

Wroblewski BM. Wear of high-density polyethylene on bone and cartilage. J Bone Joint Surg (Br) 1979; 61-B: 498-500.