BIOLOGICAL RESPONSE TO WEAR DEBRIS AFTER TOTAL HIP ARTHROPLASTY USING DIFFERENT BEARING MATERIALS.

A CLINICAL PROSPECTIVE AND RANDOMISED STUDY

Phd thesis

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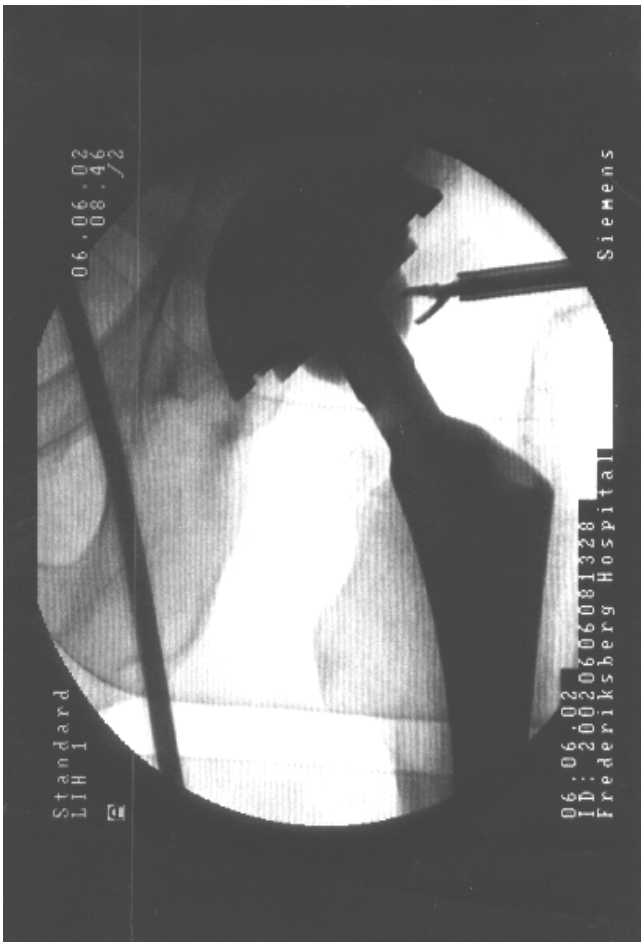

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PREFACE

The present phd thesis is based upon studies carried out at the Department of Orthopaedic Surgery, Frederiksberg University Hospital and the University of Copenhagen, Faculty of Health Sciences, Denmark in the period 2000 to 2004.

A total of three hundred patients were included in the initial randomisation. Two hundred and twenty five of these patients were included in the present thesis and seventy five were randomised to a group evaluating the polyethylene on zirconia bearing in a mono cup without screw holes (Asian cup). The three hundred patients included in these studies participate in an ongoing long term study of which this thesis is a substudy. The study is approved by the local ethical committee in 1998, (KF) 01-355/98.

The laboratory work was performed at the Institute of Molecular Pathology, University of Copenhagen, Institute of Pathological-Anatomy, Aarhus University Hospital, Institute of Medical Anatomy, University of Copenhagen, Department of Pathology, Hvidovre Hospital, The Parker Institute, Frederiksberg University Hospital, during my employment as research fellow at the Department of Orthopaedic Surgery, Frederiksberg University Hospital, Denmark.

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Vis comica!

ABBREVIATIONS

ANOVA .....Analysis of variance

bFGF .....Basic fibroblast growth factor

BMD .....Bone mineral density

CoCr .....Cobalt – Chrome

CT .....Computer tomography

CV .....Coefficient of variation

DEXA.....Dual-energy x-ray absorption

ELISA.....Enzyme Linked Immuno Sorbent Assay

GA .....Glutaraldehyde

GM-CSF ..... Granulocyte-macrophage colony stimulating factor

IGF_I .....Insulin like growth factor

IL-1 .....Interleukin - 1

IL-6 .....Interleukin - 6

IL-8 .....Interleukin - 8

IL-10 .....Interleukin - 10

IL-11 .....Interleukin - 11

LM .....Light Microscope

M-CSF .....Macrophage colony stimulating factor

MIREDIF .....Minimal relevant difference

OPG .....Osteoprotegerin

PCR .....Polymerase chain reaction

PDGF .....Platelet-derived growth factor

PE .....Polyethylene

PET .....Positron Emission Tomography

PGE-2 .....Prostaglandin E2

PMMA .....Polymethyl methacrylate

RANK .....Receptor activator of nuclear factor-κB

RANKL .....Receptor activator NF-κB ligand

RT .....Room temperature

SD .....Standard deviation

TEM .....Transmission electron microscope

TGF-β .....Transforming growth factor β

THA .....Total hip arthroplasty

TNF-α .....Tumour necrosis factor alpha

TRAP .....Tartrate resistant acid phosphatase

UHMWPE .....Ultra high molecular weight polyethylene

VEGF .....Vascular endothelial growth factor

ORIGINAL PAPERS

This phd thesis is based on the following studies:

I. Nygaard M., Zerahn B., Bruce C., Søballe K., Borgwardt A. Early periprosthetic femoral bone remodelling using different bearing material combinations in total hip arthroplasties. A prospective randomised study. *European Cell and Materials.* 2004;8:65-73.
http://www.ecmjournal.org/journal/papers/vol008/vol008.htm

II. Nygaard M., Elling F., Bastholm L., Søballe K., Borgwardt A. No difference in early cellular response of the pseudo-synovial membrane after total hip arthroplasty: comparison of 3 combinations of bearing materials.
Acta Orthop. 2006 Jun;77(3):402-12.

III. Nygaard M., Bastholm L., Elling F., Søballe K., Borgwardt A. Ultrastructural localisation of wear particles in biopsies from patients one year after total hip arthroplasty. *Submitted*

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INTRODUCTION

Osteoarthritis of the hip

Osteoarthritis of the hip can be idiopathic or secondary to osteonecrosis, trauma, sepsis, or rheumatoid arthritis. The prevalence of osteoarthritis of the hip is 3% to 6% in Caucasians and the prevalence has been the same for four decades [1]. Without treatment, the condition will develop into joint destruction, reduced mobility, pain, and reduced quality of life.

Historical review of hip implants

Several surgical methods were introduced in attempts to relieve pain from hips with osteoarthritis. Early in the 20th Century the attempts were excision of the joint surfaces and replacement with either organic or inorganic materials [2]. The results were usually rigid or instable joints. Hemiprosthesis were also practised. In 1938, Smith Petersen developed an acetabular cup and in the 1940-ties Moore and Thompson developed prosthesis to replace the femoral head [2]. The overall problem with the hemiprosthesis was a destruction of the opposite joint surface.

Total hip arthroplasties with low friction was introduced in the 1950-ties. Charnley introduced a stainless steel femoral component articulating with a polytetrafluoroethylene acetabular cup. However, the 300 arthroplasties implanted between 1958 and 1961 lasted only a few years because of excessive wear and penetration of the femoral head through the acetabular cup [3]. In 1962 Charnley was introduced to polyethylene and the wear tests were encouraging compared to polytetrafluoroethylene. Charnley decided to test the biocompability of this new material.

In the early 1960-ties, Charnley introduced polyethylene articulating against a stainless steel femoral head with a diameter of 22 mm [4,5]. The idea was to use a “synthetic articular cartilage” and self-curing acrylic cement to anchor the femoral stem and the socket [4].

The cementing technique and the use of acrylic cement was originally introduced by Haboush in 1953 [6]. However, the fixation failed because it was done to the cut end of the bone [6]. Charnley introduced the cementing method into the femur, inserting filler which created a close contact between the stem and the bone. The principles of this method are still used today.

Replacement of both femoral head and acetabular component was at the same time introduced by McKee and Watson-Farrar [7]. Initially the McKee prosthesis was made of steel, but somehow this material failed and the implants became loose in less than a year [7]. Later, both bearing components were made of a CoCr alloy and 94 % of the first 50 cases were excellent or good at a two year follow-up [7]. Sivash also pioneered a metal-metal (steel) couple at the time [8].

The metal-on-polyethylene couple had better early clinical performance and implant survival so the metal-metal couple was mainly abandoned. Factors that led to the abandonment of the metal on metal bearings were among others concerns regarding carcinogenesis and metal hypersensitivity, but also high infection rates, increased strain rates in periprosthetic bone, and fatigue fractures of the acetabular floor [9].

The basic principles of Charnleys low friction articulation have remained the golden standard bearing combination in total joint arthroplasty for 40 years although both size of the head, alloys, and shape of the components have been modified.

Today total hip arthroplasty benefits 900.000 patients with hip disorders every year. The total hip arthroplasty now provides pain relief, and an acceptable activity level, and increased quality of life in 90-95 % of the operated patients [10,11].

Epidemiology of total hip arthroplasty

Approximately 6.000 -7.000 hip arthroplasties are performed in Denmark each year. The incidence of primary total hip arthroplasty has in Denmark increased from 72 in 1995 to 110 in 2003 [12,13]. In Scandinavia, the total number of hip arthroplasties is approximately 25.000 per year [13-17].

In The Danish Hip Arthroplasty Register, 55.547 hip replacements were registered during the period 1995-2003 [12,13]. A total of 47.258 were primary hip arthroplasties (84.1%) and 8.289 were total hip revisions (14.9%).

The reasons for revision were registered. Aseptic loosening was the most commonly reported cause, namely 3.874 (65.9%) of the total number of revisions. The second most frequent cause was dislocation namely 771 (13.0%) and the third was deep infection 371 (6.2%) [12,13].

Revisions are time consuming, expensive and very inconvenient for the patient. The mean operation time for a revision was 134 minutes compared to 78 minutes for a primary hip arthroplasty [12]. The risk of infection, dislocation, decreased mobility, and chronic pain is higher after a revision compared to a primary hip arthroplasty [13,18].

The age of the patient has an influence of the rate of revision. A 12-year follow up including 128.926 revisions was presented in The Swedish National Hip Arthroplasty Register [19]. The revision rate increased with decreased age: 3 - 7 % for those older than 75 years, 7 - 12 % for those aged 60 -75 years, 13 - 22 % for those between 50 - 59 years, and 18 - 30 % of those younger than 50 years at the time of surgery. Male patients had the highest revision rate in all age groups.

The mean age of patients in the Danish Hip Arthroplasty Register was 68 years, 20.9 % of these patients were younger than 59 years [12,13].

For these reasons total hip arthroplasty has been a controversial subject when it comes to younger patients [13,20-22]. Reports of these problems may cause a delay of the primary hip replacements in spite of relevant indications.

The number of primary total hip arthroplasties and the number of young patients operated are both increasing, thus an overall increase in the rate of revision can be expected.

Reducing the rate of revision, are for these reasons of great importance for the long-term results of hip arthroplasties especially in young and active patients.

History of aseptic loosening in hip arthroplasty

Aseptic loosening is a result of excessive periprosthetic bone loss resulting in loss of integrity between bone and implant.

The early stage of aseptic loosening may be asymptomatic. Later the hip implant loosens and the symptoms are pain, reduced mobility, periprosthetic radiolucent zones, and consequently the implant must be revised.

Charnley was the first to describe a radiolucent zone around the implant [23]. Initially Charnley suggested that the lucent zones were caused by infection. Later he described macrophages and cysts in the tissue related to a failed femoral stem [24].

In 1976 Harris et al described an extensive localized bone resorption on x-ray within the femur of four patients and suggested the presence of infection or tumor [25]. During revision of the femoral components, he found only slight loosening. The periprosthetic tissue was examined histologically and Harris discovered sheets of macrophages, a few giant cells, and birefringent material. He suggested a benign, non-infectious tissue response in relation to the femoral components.

In 1977, Willert reported that the newly formed capsules surrounding artificial joints contained small particles of prosthetic material (plastic, metal) [26]. He suggested that the particles could induce a formation of granulation tissue and foreign-body giant cells [26].

In 1983, Goldring et al presented a more detailed biological investigation [27]. Bone-cement interface was retrieved from twenty patients with aseptic loose hip arthroplasties. Goldring described synovial-like cells, absence of inflammatory cells and that the tissue had a high capacity to produce PGE-2 and collagenase. It was suggested that this reaction might explain the progressive lysis of bone seen in periprosthetic areas [27].

In 1986, Jasty et al reported four cases of extensive localized bone resorption in cemented total hip replacements. None of the hips showed evidence of infection. The tissue from the regions of osteolysis showed sheets of macrophages and foreign-body giant cells invading the femoral bone [28].

In 1987, Jones et al suggested that the properties of the bone cement also contributed to the pathologic state of loosening and suggested that "cement disease" might exist [29].

Periprosthetic tissue

The periprosthetic tissue refers to the pseudosynovial membrane and the interface. The pseudosynovial membrane constitutes the new capsule tissue.

The interface can be separated in the implant - cement interface and the cement - bone interface and in cementless implants, the bone-implant interface. Fig. 1.

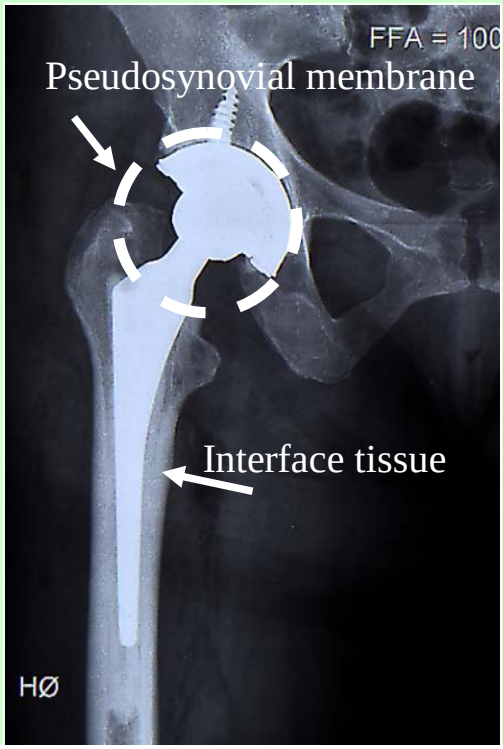


Fig. 1 illustrates the location of periprosthetic tissue. Following a total hip arthroplasty a new capsule, the *pseudosynovial membrane*, develops in the wound cavity of the implant and replaces the original capsule.

The *interface tissue* represents the tissue along the stem and can be separated in a bone-cement and a cement-stem interface. If the implant is cementless, the interface tissue represents the bone-stem interface.

The normal synovial membrane consists of a layer of synovial cells and subsynovial tissue. Following a total hip arthroplasty a new capsule, the pseudosynovial membrane, develops in the wound cavity of the implant and replaces the original capsule [26]. As early as one month after a total hip arthroplasty a simple layer of granulation tissue has been observed in the new capsule [30]. Two and a half months postoperatively, flat synovial-like cells have been identified and 7 months postoperatively a fully synovial-like membrane was developed [30]. The new pseudosynovial membrane appears more primitive with a more irregular synovial cell layer. Fibroblasts, macrophages, mast cells, endothelial cells, and lymphocytes have been observed in the membrane [31].

Investigations of the biological response to wear particles have largely been focusing on the interface tissue [32-34]. The particle-host reaction is often investigated in revised implants and at the end state of the chronic inflammation [34-37].

Wear particles in hip arthroplasties

The wear particles are defined as the lost materials produced at the bearing materials during movement. Wear particles of other materials, such as cement, small bone fragments or metal from the femoral stem may act as a third body or grindstone when sited between the bearing materials. In such case the wear rate may be accelerated.

The particles can migrate and have been identified distantly from the bearing materials distal to the stem [38]. The transport mechanism along the interface may be a pumping effect of fluid during movement, thus generating a cyclic loading between effective joint space and the articulating materials [39] (Fig. 2). Additionally, particles have been found in the paraaortic lymph nodes and the liver [40] *(*)*

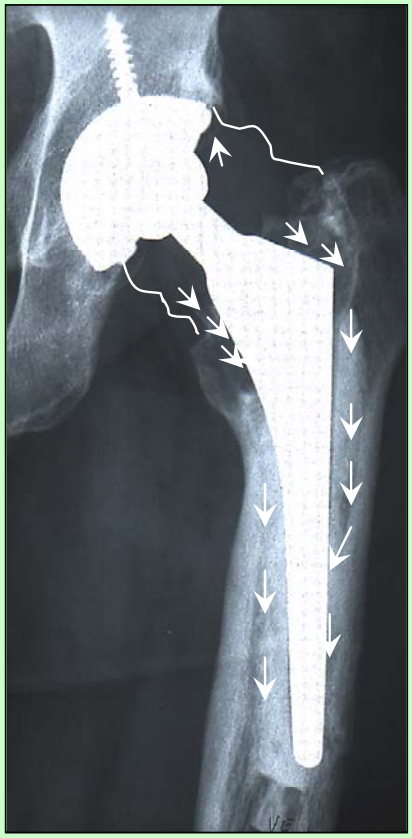


Fig. 2. Particles can at time of revision be found at the distal part of the stem.

The figure illustrates the suggested direction by which the synovial fluid may transport the particles from the bearing surfaces to the implant-cement-bone interface.

(*) An introduction to commonly used bearing surfaces, friction and wear, and different wear modes are introduced in Appendix A.

Cellular response to wear particles

Today it is well accepted that wear particles from the implant are one of the causes involved in the pathogenesis of aseptic loosening of hip arthroplasties by granulomatous lesions [34,35,41-43]. The putative etiologies are described below.

Subsequent to a total hip arthroplasty some patients develop an aseptic chronic inflammation around the implant [30,34,35]. The pathogenesis of this course remains by and large unknown [44-49]. It is believed that a biological response of the host to the implant material is one of the causes [44,50-54]. The response can be demonstrated in the pseudosynovial membrane or at the interface tissue and the various cells in these tissues may all be involved.

In previous studies the histological findings encompassed have been particles, sheets of macrophages and granulomatous inflammation in tissue from aseptic loose implants [55-59]. Thus, the interaction between macrophages and the wear particles has been the major subject for investigation.

Monocytes/macrophages

Initially, accumulated particles attract macrophages that subsequently ingest the foreign body material in order to eliminate it [60]. Macrophages with intracellular foreign body material are activated and the activation may develop into several patterns 1) activated macrophages may form granulomas 2) cause osteoclast independent bone resorption, or 3) produce bone-resorbing mediators *(*)*. These mediators may either a) activate or inhibit the activity of bone remodelling cells or b) initiate the monocyte-macrophage differentiation into osteoclast-like cells.

1) A granuloma is a focal area of granulomatous inflammation and is a distinctive pattern of the chronic inflammation [61]. The granuloma is the response to a foreign body too large to be phagocytized [61]. When the macrophages fail to remove the foreign body from the host, the cells aggregate to wall off the foreign body thus forming a granuloma. The material responsible for fusion is suggested to be either the particles or the denatured macromolecules formed by the inflammatory process [62]. In some instances, the granuloma cells fuse forming a foreign body giant cell.

(*) Some of the cell mediators known to stimulate or inhibit bone resorption are listed in Appendix B.

Accumulation of macrophages and the formation into granulomas or giant cells represent the outcome of a complex interaction between the organism and the particles. The cascade is modulated by numerous enzymes and cytokines produced by periprosthetic cells [63].

The severity of the granulomatous response has been correlated with the degree of periprosthetic bone resorption and to the degree of wear debris [64]. Thus, there is a reason to believe that the interaction between particles and macrophages is pathogenetic in the loosening of the implants.

It is not clear when the granulomatous inflammation begins, but macrophages with intracellular ceramic and polyethylene particles have been demonstrated in the pseudosynovial membrane as early as seven months postoperatively [57]. The implants had a history of loosening or impingement.

2) Macrophages activated by intracellular particles can *in vitro* result in low grade bone resorption when the macrophages are placed on bone surface [65]. Macrophages and giant cells retrieved from joint capsules of failed hip arthroplasties are both capable of producing small resorption pits of the bone surface [65].

3) Increased bone resorption can be the result of either increased activity or increased number of the bone resorbing cells.

a) Activated macrophages are capable of producing numerous mediators that stimulate or inhibit fibroblast, endothelial cell, osteoblast, and osteoclast activity in the periprosthetic zone *(*)*.

b) Physiological and pathological bone resorption can be induced by monocytes, macrophages, giant cells, and osteoclasts. Monocytes and macrophages are precursors for multinucleated giant cells with the characteristics of mature osteoclasts, inducing lacunar bone resorption [66-68]. It has been suggested that osteoclasts and giant cells are phenotypically and functionally identical [69].

The differentiation of monocytes and macrophages is stimulated by osteoclast differentiation factor and M-CSF secreted by macrophages, fibroblasts, endothelial cells, osteoblasts, lymphocytes, and mast cells [66] the process is inhibited by osteoprotegerin [66].

When the physiological balance between bone resorption and bone formation is interfered by increased bone resorptive mediators, the outcome is accelerated bone loss resulting in loosening of the implant.

(*) Some of the cell mediators known to stimulate or inhibit bone resorption are listed in Appendix B.

Fibroblasts

While the macrophage response to particles and its role in aseptic loosening has been extensively studied, information regarding fibroblasts is limited. Fibroblasts represent a considerable quantity of the periprosthetic tissue, but only few studies examine the role of this cell in the chronic inflammation. Fibroblast have the capability of phagocytosis [70-72] and intracellular particles have been found in the periprosthetic fibroblasts of aseptic loosened hip arthroplasties [71,73]. Thus, particles have been suggested to activate fibroblasts and later be a part in the inflammatory process [74].

The fibroblasts are capable of increasing bone resorption by different pathways 1) activated fibroblasts may stimulate or inhibit the activity of bone remodelling cells *(*)* 2) increase the number of bone resorbing cells 3) direct osteoclasts-independent bone resorption [75].

1) Fibroblasts are *in vitro* activated by particles expressed by a dose-dependent release of IL-6 and PGE-2, both inducing bone resorption [76].

An interaction between the macrophages and fibroblasts in inflammation are integrated *in vitro*. When macrophages *in vitro* are exposed to phagocytosable PMMA particles and co-cultured with fibroblasts, the macrophage production of IL-6 is significantly higher compared to control macrophages without fibroblasts [77]. The macrophage expression of TNF-α and IL-1β is not *in vitro* influenced by the fibroblasts [77].

Whether the coupling between macrophages and fibroblasts is synergistic *in vivo* is not clear. A difference was found between aggressive granulomatosis and minor lesions in periprosthetic tissue after aseptic loosening [34]. In the zones with aggressive granulomatosis, fibroblasts were not activated suggesting a protective effect of activated fibroblasts. Without a fibroblast mediated remodelling of the extracellular matrix the macrophage mediated bone resorption may accelerate.

Basic fibroblast growth factor bFGF formation is elevated in the pseudosynovial membrane from aseptic loose implants when compared to control synovial membrane [78]. This suggests that fibroblast may contribute to bone formation.

(*) Some of the cell mediators known to stimulate or inhibit bone resorption are listed in Appendix B.

2) The fibroblast produce matrix-metalloproteinases and M-CSF [31]. The latter is an essential mediator in the macrophage differentiation into osteoclast-like cells [66]. The osteoclastogenesis may be further be supported by RANKL released from fibroblasts in the pseudosynovial membrane [79,80].

3) Fibroblasts are capable of osteoclast-independent bone resorption similar to those in early osteoclast resorption [75]. The findings are from an animal study. Whether the fibroblasts had intracellular particles is not clear.

Endothelial cells

The exact role of endothelial cells in the periprosthetic chronic inflammation and aseptic loosening is not clear. Hence the endothelial cells are metabolically active and responsive for physiological changes and cell injury [81]. The endothelial cells may be a part of a complex interaction which involves cells such as macrophages, fibroblasts, osteoblasts, and osteoclasts.

The role of the endothelial cells is suggested to be 1) production of mediators activating or inhibiting the activity of bone resorbing cells *(*)* 2) production of mediators inducing differentiation of bone resorbing cells 3) an active participant in the transportation between the tissue and circulating blood components (cellular and non-cellular) [61] 4) direct osteoclast-independent bone resorption?

1) In chronic inflammation endothelial cells increase the production of mediators such as of IL-1, IL-6, and IL-8 stimulating bone resorption.

2) Endothelial cells are producing GM-CSF [31] inducing osteoclast differentiation and OPG a RANKL receptor antagonist protein known to inhibit the osteoclast differentiation [82].

When activated with cytokines the endothelial cells can induce formation, fusion, and bone resorption of osteoclasts co-cultured with circulating human monocytic precursors [83].

3) Osteoclast precursors are transported to the site of osteoclast formation and remodelling via the vascular system before migrating to the bone surface [84].

Particles may also be transported away from the joint via the vascular or lymphatic system. The relation between particle concentration and microvessel area was evaluated in periprosthetic tissue from aseptic loose implants. A reduced microvessel area was correlated to a high concentration of particles [85]. A high concentration of particles may putatively be a result of reduced vascularisation and

(*) Some of the cell mediators known to stimulate or inhibit bone resorption are listed in Appendix B.

thus a low transportation of particles away from the tissue. Opposite may a reduced microvessel area have been caused from an excessive particle accumulation?

Macrophages challenged with titanium particles induces a dose and time dependent release of VEGF is i*n vitro* [86]. VEGF promotes angiogenesis in chronic inflammatory reactions, increases the vascular permeability, and stimulates the endothelial cell migration and proliferation.

4) Hemangiosarcomas can occasionally be found in long bones [87]. It is not clear whether endothelial cells have osteolytic capabilities.

Osteoblast/osteoclast

Bone remodelling is normally a balanced interaction between osteoblasts bone formation and osteoclasts bone resorption. Osteoblasts and osteoblasts are rarely present in the pseudosynovial membrane. Hence, the already mentioned interactions between cells induced by particles may influence the activity of these cells.

Particle characteristics

The effect of different wear particle characteristics on the macrophage has also been examined [49]. A critical particle size range for inducing phagocytosis and activation of macrophages is 0.2-10μm [49,88]. The shape and surface texture of the particle have previously been suggested to influence the cellular response [89,90]. Irregular PMMA particles induced significantly more inflammatory response than smooth particles expressed as TNF-α, PGE-2, and metalloproteinases production in a root pouch model [51].

The magnitude of polyethylene particles have been positively correlated to the number of macrophages in retrieved tissue at revision [91-93]. Further, it has been demonstrated *in vitro* that macrophages increased phagocytosis with increased concentration of particles when the particles were smaller than 2 μm in length [94].

Fibroblasts are *in vitro* sensitive to particle exposure at different concentration and sizes. Bovine synovial fibroblasts were exposed to titanium, aluminium and cobalt - chromium particles of different sizes [95]. The cell activity was estimated by 3H-thymidine uptake and the particles significantly stimulated the uptake at low particle concentrations [95]. In contrary, exposure to cobalt

particles resulted in a significant decrease of 3H-thymidine uptake independent of particle size [95]. When the particle concentration was high, all materials were toxic [95].

Other etiologies of aseptic loosening

Prosthetic stress shielding

Manufacturing of the prosthesis involves the use of different materials, prosthetic shape, and surface texture.

In the normally femur the load is transferred through the proximal part of the bone [96]. After a total hip arthroplasty, this pattern is changed and the result is according to Wolff's law (Wolff, 1892) reduced bone mass density of the proximal femur bone and sometimes increased bone mass density in the distal zone [96]. The degree of stress shielding transferred from the implant to specific bone zones depends on the biomechanical properties of the cement and the implant and can induce more or less changes of the bone mineral density compared to the preoperative level [97].

Method of surgery (operation, method of fixation)

Preparation for the implant can be more or less traumatic to the surrounding tissue as bone cells and the vascular providence. Further, the surgeons positioning of the implant is of importance for future biomechanical function, wear production, and stress shielding. In a follow-up study of McKee-Farrar prosthesis Zahiri et al found that loose implants had biomechanically disadvantaged compared to implants that demonstrated long-term survival. He suggested that poor biomechanics could have resulted in an increased joint reaction and thus contributed to the early loosening. [98].

Vascular injury may result from the reaming process and thermal injury from hardening of the cement. To what extend the vascular injury influences the bone resorption is to our knowledge not clear. Previous studies have found that the periprosthetic blood flow was significantly reduced in the proximal femur when measured immediate postoperative [99,100]. Further, the vascularity was reduced in the periprosthetic tissue from aseptic loose implants when compared to normal synovial membrane [101]. It was suggested that the decreased vascularity could result in an insufficient osteointegration of the implant and an increased risk of loosening [34].

Endotoxin

Endotoxin contamination of the biomaterials may be underrated. Endotoxin is a component present in the bacterial cell wall inducing the inflammatory response to the bacteria. It has been suggested that endotoxin on the surface of the particles may induce phagocytosis and an inflammatory response.

An *in vitro* study examined whether adherent endotoxin on the wear particles is responsible for inducing osteoclast differentiation as well as production of IL-1β, IL-6, and TNF-α. Removal of adherent endotoxin almost completely inhibited the responses to titanium (Ti) particles by both murine bone marrow cells and human peripheral blood monocytes and that endotoxin removal reduced particle-induced osteolysis by 50 -70%. [102].

The endotoxin can probably adhere to the particle at any time during production or even in the patient at a stage of infection.

Skoglund et al applied endotoxin-contaminated or uncontaminated high-density-polyethylene particles to bone tissue in rats [103]. The contaminated wear particles showed a dramatic bone resorption after one week compared to uncontaminated specimens that showed no bone resorption. After 21 days, the area with bone resorption healed. They concluded that endotoxin was a major concern. The exact influence of endotoxin on long-term survival is yet not known.

Host status

The individual host is also of importance regarding long-term survival of the implant. Age, gender, bone quality (osteoporosis), medication, hormone status, weight, and activity level may all play important rolls in the development of loosening.

Allergic reactions to components of the implant may also induce a response of the host to the implant. The prevalence of dermal metal sensitivity in patients with loose hip arthroplasties is higher compared with the general population [104]. It remains unclear whether metal sensitivity is a contributing factor to implant loosening [104].

Current improvements to aseptic loosening

The findings presented in this review have especially contributed to the need for more wear resistant bearing materials. The hypothesis has been that a low wear rate would reduce the number of recruited macrophages and thus reducing the cascade of cellular interaction and accelerated bone resorption.

Alternate bearing materials such as CoCr on CoCr and alumina on alumina, were developed in an attempt to minimise wear production and by this means reduce the foreign body response [36]. The wear rate of these bearings is reduced significantly compared to the traditional polyethylene – metal bearings [9,105-107]. Fig. 3.

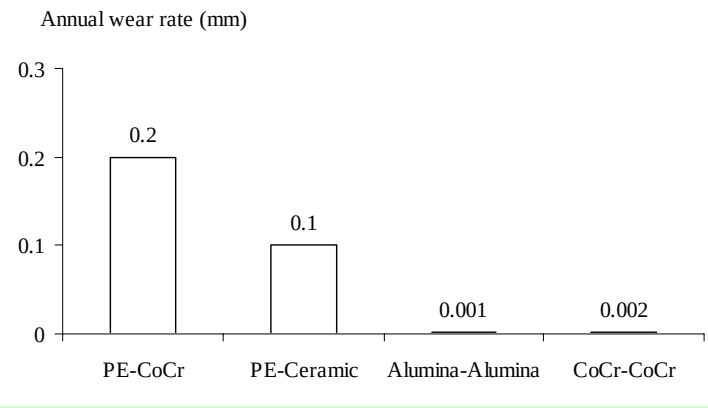


Fig. 3. The wear rate of the alternate bearing surface combinations compared to the traditional polyethylene – metal bearings.

Highly cross-linked polyethylene represents a new class of polymers and is achieved by generating free radicals along the long chains that constitutes the polyethylene molecules. Subsequently, the free radicals combine with each other, thus forming carbon-carbon covalent bonds. These bonds are cross-linked [36]. The cross-linked polyethylene has proven to be very wear resistant when compared to conventionally polyethylene [108].

Coating of the bearing materials with extremely wear resistant materials such as Diamond-Like Carbon has been introduced as subjects for improvement [109]. This material has an extreme hardness and a low friction coefficient [109]. The wear rate of polyethylene when tested against Diamond-Like Carbon was

reduced when compared to metal and alumina [109]. The inflammatory response to particles of diamond may be reduced when compared to polyethylene and CoCr [110].

The term cushion bearings is the combination of a hard bearing femoral head articulating with a smooth conform liner with lubrication [111]. Materials suggested for this purpose have been non-porous polyurethanes and porous hydrogel. The concept has been to produce a more flexible layer to promote lubrication in the joint, thus to approach the natural synovial joint. A major problem to this approach has been to incorporate the soft liner into the metal backing of the metallic acetabular shell [111].

Other attempts to enhance bone ingrowth and reduce osteolysis have been regarding medical treatment using osteoclast inhibitors such as bisphosphonates.

Summary

The fact is that the annual wear rate of the alternate bearing material is significantly reduced compared to the traditional bearings. The bearing material combinations used in the present study have all been used for decades in total hip arthroplasties with good results.

Though, aseptic loosening has been demonstrated with all bearing combinations are prospective studies with these bearing combinations rare.

In addition to wear rate, previous *in vitro* and *in vivo* studies have demonstrated that the cellular response and capability to bone resorption varied with different characteristics of the particle [88,94,112].

Therefore, it can be assumed that various bearing materials even with reduced wear rates may induce different and unpredictable biological responses. How these mechanisms are controlled is not clear. The possible combinations of particle number, size, distribution, surface texture, surface area, host response and chemical behaviour , and the individual host response make the investigation of this subject very complicated.

The significant reduced wear rate in these bearings cannot predict the *in vivo* cellular response of the individual patient or the clinical outcome in a cohort of patients of hip implants. The numbers of parameters involved in biological response are too numerous and complex.

One method to evaluate the host response to these different bearings is to perform a clinical prospective and randomised study with relevant bearing surface materials.

AIMS

The three bearing combinations tested were Polyethylene-Zirconia, CoCr-CoCr, and Alumina-Alumina.

Study I

The aim of the study was to examine the pattern of periprosthetic bone remodelling and compare the mean change in the periprosthetic bone mineral density by DEXA when using the three different bearing material combinations.

Study II

The aim of the study was to examine the cellular response to the three different bearing material combinations by estimating the volume fraction of macrophage, granuloma, and endothelial cells in the pseudosynovial membrane by point counting using light microscopy.

Study III

The aim of the study was by transmission electron microscope to examine the ultrastructural morphology of cells and particle localisation in the pseudosynovial membrane in the three different bearing material combinations.

Study IV

The aim of the study was by to quantify and compare the concentration of cytokines in the pseudosynovial membrane flow cytometry and ELISA when using three different bearing combinations. The analysis has not been completed.

PATIENTS AND METHODS

Patients

The present thesis is a prospective and randomised trail. Two hundred and twenty five patients participated in the present studies (139 females, 86 males) and had a primary hybrid total hip replacement during the period from January 2001 to January 2003 at the Orthopaedic Department, Frederiksberg University Hospital. These patients participate in an ongoing long term survival study of hip arthroplasties with different bearings. Details are specified in the preface section.

The patients participating in the trial had primary osteoarthritis, rheumatoid arthritis, or avascular necrosis of the femoral head. The patients had previously given their informed consent. Exclusion criteria were: under 18 years of age, dementia, active infection, revision arthroplasty, marked bone loss which could prevent adequate fixation of the device, severe vascular insufficiency of the affected limb, severe instability or deformity, abnormal gait due to other reasons e.g. poliomyelitis.

After the operation, all the patients were informed about the bearing material used.

Bearing materials

Patients were randomly distributed to receive one of three bearing material combinations (Table 1). Appendix A presents more details of these bearing materials.

Table 1. Bearing material combinations

Articulation	RingLoc insert	Modular head[5]
I	Polyethylene[1]	Zirconia[2] (ZrO_2)
II	CoCrMo[3]	CoCrMo
III	Alumina[4] (Al_2O_3)	Alumina (Al_2O_3)

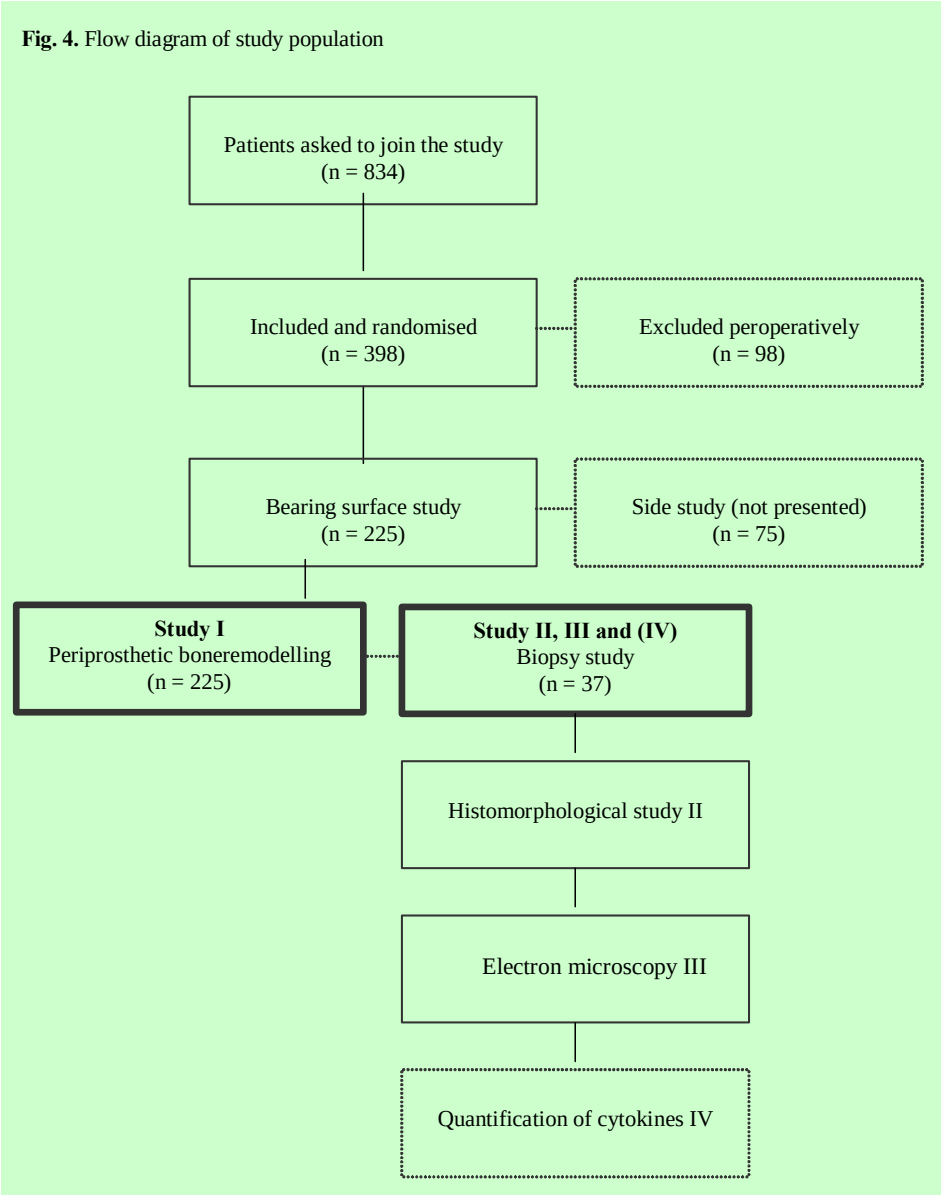
1) ArCom, Biomet, Warsaw, Indiana, USA; 2) ZrO_2 head Biomet Merck, Warsaw, Indiana, USA; 3) M2a, CoCrMo Alloy, ISO 5832-12 1996 and ASTM 1537, Biomet Merck, Warsaw, Indiana, USA ; 4) Ceracup, Biolox Forte, Biomet, Warsaw, Indiana, USA; 5) 28 millimetres in diameter

Randomisation

The patients were randomised to receive one of three bearing material combinations. Polyethylene - zirconia (n = 78), CoCr - CoCr (n = 71), alumina - alumina (n = 76).

The randomisation was performed by a computer (MS Excel 2000 - Rand programme) and the randomisation number was saved in a closed envelope that was opened prior to the operation. A flow diagram illustrates the study population. Fig. 4.

Fig. 4. Flow diagram of study population



Acetabular component and stem

All patients had similar cementless acetabular components, Universal RingLoc®, plasma sprayed porous coated with screw holes (Ti-alloy, Biomet, Warsaw, Indiana, USA). The acetabular components were inserted by a press fit method. Screws were used when needed.

The stems were Bi-Metric collarless stem, (Ti-alloy, Biomet, Warsaw, Indiana, USA), cemented with Palacos R-40 with Gentamicin® (Merck).

One year follow-up

One year after insertion of the implant, a follow-up examination was performed in the group of 225 patients.

Study I

Periprosthetic bone remodelling

Bone mineral density (BMD) was determined in 225 patients: polyethylene-zirconia (n = 78), CoCr-CoCr (n = 71), or alumina-alumina (n = 76), with DEXA (Lunar DXP IQ#7160, Lunar corporation, Madison, WI, USA; Software DPX-IQ X-Ray Bone Densitometer with SmartScan ^{TM} Version 4.7e).

The periprosthetic BMD of the operated hip was measured within one week postoperatively. The procedure was repeated after one year.

Bone mineral density was measured with Dual-Energy X-ray Absorptiometry in seven Gruen zones adjacent to the femoral implant [113]. See Appendix C (Paper I) for details of the procedure.

Statistics

The sample size was calculated by the equation (significance level 0.05; power 0.8).

$$n_1 = n_2 = 2(t_{2a} + t_b)^2 SD^2/MIREDIF^2$$

$$n_1 = n_2 = 2(1.96+0.84)^2 0.2^2/0.1^2 = 63$$

The calculated n was added with 12 patients in each group in the case that some patients were lost to follow-up. Statistical comparison of the groups was performed with ANOVA and students t-test (10.05 SPSS Inc. Chicago). The data were normal distributed.

Return for biopsy

A total of 37 patients (≅ 16%), 18 females, and 19 males volunteered to participate in a transarthroscopic biopsy procedure. Polyethylene – zirconia (n=15), CoCr – CoCr (n=9), and alumina – alumina (n=13)

Study II

Histomorphological study

Two biopsies from each patient were used for estimation of the volume fraction of, macrophages (CD68), granulomas, and endothelial cells (CD34) in the pseudosynovial membrane by a point counting technique using light microscopy.

Biopsy 1 was cut in 2μm semi-thin plastic sections and stained with toluidin blue for quantification of granulomas.

Biopsy 2 was embedded in paraffin for immunohistochemistry: mouse monoclonal anti-human IgG's used as primary antibodies: CD68, macrophage/monocytes (dilution 1:500, M0814) and CD34, endothelial cells (dilution 1:200, M7165) from DAKO, Denmark. See Appendix C (Paper II) for details of the procedure.

Statistics

Statistical comparison of the groups was performed with Mann Whitney test for independent samples of non-parametric data (SPSS for windows).

Study III

Electron microscopy

The aim of the study was by transmission electron microscope to examine the ultrastructural morphology of cells and the particle localisation in the pseudosynovial membrane in the different bearing combinations.

The biopsies for the morphological study were processed according to standard procedures for electron microscopy and the sections were examined in a JEOL (JEM1010) electron microscope.

Toluidin blue stained sections were examined for areas with granulomas by light microscopy. Granulomas were defined as spherical accumulations of macrophages (≥ 4) with or without surrounding collagen fibres.

Macrophages were demonstrated as CD68 positive by immunostaining in study I. In biopsies without granulomas, cell rich areas were chosen.

Endothelial cells were identified in study I by CD34 positive staining [114]. In the present study the endothelial cells were identified by the presence of Weibel – Palade bodies.

Two biopsies in the polyethylene-zirconia group, one in the alumina group, and one in the CoCr group were excluded because of failed fixation. See Appendix C (Paper III) for further details.

Fabricated particles

For comparison with the observations in the biopsies, alumina and CoCr particles fabricated in a hip simulator and studied by TEM.

Study IV

Quantification of cytokines

A fourth study in the thesis was to quantify the concentration of cytokines in pseudosynovial membrane biopsies. These biopsies were taken in the same procedure and from the same patients as in study II and III, but the analysis was not completed.

More than a year was used to develop a method of flow cytometry to measure these cytokines. The flow cytometry method was attractive since the biopsies are relatively small and the method facilitated the measuring of a high number of cytokines in very small specimens. However, the method did not succeed and the ELISA method was chosen for some of the cytokines.

The ELISA method was preferred instead of an immunohistochemical method that is at best semiquantitative. Because of problems in developing the method of flow cytometry the results this part of the study is delayed.

Regarding synovial fluid it was only possible to get an adequate amount from nine patients so this part of the study could not be performed.

METHODOLOGICAL CONSIDERATIONS

The section “methodological consideration” is a brief reading regarding the methods employed in the publications and the thesis.

A discussion of the methods used for obtaining and evaluating the results is separated into:

1. Study designs
2. Periprosthetic bone remodelling
3. Histomorphological study
4. Electron microscopy

Various methods for evaluation of the subject of this thesis have previously been chosen.

Study designs

To evaluate the biological response to implants with various bearing materials in humans a clinical study was performed. The study was a one-centre study. A total of 275 patients participated in the investigation. The patients followed criteria’s of inclusion and exclusion as described in the section “Patients and methods”. The main group and long term study is specified in the Preface section.

The patients were randomised into three groups and their response to the implant was evaluated at a one year follow up visit. The study used the same type of implant for all patients. The only variable was the type of bearing material combinations.

The calculation of the sample sizes used in the studies are specified in the section “Patients and methods” and in Appendix C (Paper I-III).

The advantage of a clinical study is that it reflects the impact of particles that are gradually produced (fast or slow) and perhaps also gradually removed.

The response to implant wear in humans has been investigated to a great extent in retrospective studies at time of revision of the implant. These studies have contributed with information regarding the chronic inflammation and aseptic loosening, but tissue derived from a failed implant may not represent the entire cohort operated. Further, the use of different prosthetic designs and materials make the

results of these studies very difficult to compare. These studies only represent the end stage of the osteolytic process. At that time a complex cascade of cellular interactions may have taken place.
Clinical difficulties in evaluating the cellular response to particles have contributed to development of animal studies and *in vitro* methods.

A great deal of published animal studies employing a single exposure of a bolus containing the particle in question. The site of the bolus injection may reflect a situation with focal osteolysis or aggressive granulomatosis since the concentration of particles is extremely high. Additionally, animal studies are often testing the characteristics of different wear particles in a period of a week [90] or months. However, animal studies are valuable, and the reproducibility is high. Controls are simple and the animal studies have contributed with many informative conclusions to the understanding of the biological response to wear particles. Results from an animal study are only relevant for the actual study and may not uncritically be transferred to humans.

The *in vitro* response of the cell to foreign bodies is evaluated by measurements of secretory products, cellular accumulation, differentiation or fusion, or capability to induce lacunar bone resorption and phagocytosis. However, these studies lack the presence of inhibitors and the possibility to attract other cell types.

The time range from particle exposure to evaluation is huge when comparing the different study methods mentioned. *In vitro* studies are evaluating the cellular activity within hours or weeks. In animals studies the response is often evaluated weeks or months after particle exposure. The results are impossible to compare with long-term exposure in humans.

Periprosthetic bone remodelling

DEXA scan has made it possible to measure bone mineralization adjacent to the metal implant and to follow the periprosthetic bone remodelling longitudinally.
DEXA scan is a sensitive method that provides the means for evaluating minor changes not visible on x-ray. This is especially relevant in the initial post operative phase since x-ray requires more than 30% bone loss before detection is possible [115]. X-ray does not allow a calculation of the BMD.

The result of the study depends of the reproducibility of the method. Different errors may be related to the DEXA method. Reproducibility of the DEXA was assessed by 1) double scans and 2) phantom rotation study.

1) To evaluate the reproducibility of the method, double scans were performed in 23 patients.

The patients were repositioned between the two scans. Prior to the measurements, the region of interest was defined as the Gruen zones and the scan window was from the proximal part of the implant to 20 lines distal to the tip of the stem (approx. 1 cm).

The DEXA computer software measure and calculate the bone mineral content (g), the area (cm^2), and the BMD (g/cm^2) using.

From the measurements the coefficient of variation between two scans was found to be within the range from 2.2 to 4.7% depending of the region. The highest coefficient of variation was found in zone seven. These findings demonstrated a high reproducibility important for the long term study and a capability to detect minor changes in BMD.

2) Since the BMD is most likely to change when the femur is rotated, the reproducibility depending on rotation was evaluated.

On a cadaver femur with an inserted femoral component repeated measurements were performed. The cadaver femur was placed in a water bath and scanned seventeen times from a fifteen degrees outward rotation to a fifteen degrees inward rotation with increments of five degrees.

Maximal changes was found in zone seven whereas the BMD increased with 16.1 % at 15 degrees inward rotation and decreased with 10.3 % at 15 degrees outward rotation compared to neutral position. This error from rotation was minimised by placing all patients with the leg fixated in neutral position and with an extended leg.

Systematic errors may have been to a smaller degree of rotation and irregular shape of the bone.

The cohort in the present study did not differ in BMD in any region of interest when compared immediately postoperatively.

Placement of reference points during analysis may also be a bias. Analysis in the study was performed by an experienced team of three.

Surgery alone influences the BMD and the bone loss may be overestimated if the DEXA scan is made prior to the operation or if the opposite femur is used as control. To overcome this bias, the BMD of the operated leg served as its own control immediate and one year after the operation.

Fig. 5 illustrates the DEXA method used for BMD measurements.

Seventeen patients in the study had an inconclusive DEXA scan. The inconclusive scans were mainly seen in patients with a high BMD. The reason for this is most likely, that the software was incapable of differentiating the titanium stem from bone with a high BMD. This may be explained by a total block of the photo beam.

The DEXA apparatus uses x-ray beams which are filtered to allow two energies to be produced. These two energies are reduced differently in soft tissue and bone. The radiation transmitted through the tissue is then measured by a detector and the BMD is calculated. Metal completely blocks the photon beam of the apparatus. This block causes that bone lying anterior and posterior to the metal stem will be disregarded and only the bone lateral to the stem will be included in the measurements.

Hypothetically, the photo beam may to a certain degree have been blocked by a high BMD as well as the implant. In such case it is impossible to determine the position of the stem and the BMD can not be calculated. Even by manual evaluation it was impossible to distinguish bone from stem in these patients and the scans were excluded. An effort to develop a software solution to these technical problems is provided by the manufactory, thus enabling manual correction of previous scans.

Patients with a low body mass index could also be difficult to evaluate. The difficulties may be explained by lack of a soft tissue reference. These patients had rice bags placed along the leg and the speed of the scan was reduced improving the measurements.

The equipment and methods used are described in details in Appendix C (Paper I) and illustrated in Fig. 5.

Histomorphological studies

Biopsies were taken to evaluate whether the bone changes could be due to a tissue inflammation. The biopsy method was a useful approach for a qualitative and quantitative examination of the periprosthetic tissue response in well-functioning hip implants.

The biopsies were retrieved one year after implantation and it was documented that particles were present. Hence, the biological response at this stage can be evaluated.

The present study has demonstrated a chronic inflammation in the pseudosynovial membrane one year after implantation of the implant. It is not clear when the granulomatous inflammation exactly begins.

Light microscopy was used to study the morphology quantitatively and qualitatively. Cell types were verified by immunohistochemical staining. To further analyse the localisation of the particles TEM was used.

Potential errors may occur during 1) biopsy acquisition 2) preparation, and 3) evaluation

1) The biopsies were taken transarthroscopically through an anterolateral route using a biopsy needle and a coaxial needle. Fig 6.

To optimize the reproducibility, all biopsies were taken from the lateral area of the pseudosynovial membrane. In some occasions the specimens contained mainly fat tissue. The fat probably derived from the channel through the subcutis. These biopsies were not evaluated.

Problems with the biopsy method are a) the risk of infection in the tissue surrounding a well-functioning implant. Hence, it is not tempting taking biopsies too often. The risk of infection has been estimated to be less than one per mille. The risk of infection of a primary hip arthroplasty is > 0.5%. The duration of this operation is longer and the incision is considerably larger. The arthroscopic biopsy takes approximately 5 min b) it allows only evaluation of a limited area of the pseudosynovial membrane.

Optimally, the study should have encompassed biopsies from all 225 patients. Nevertheless, the method gave the possibility to study the early cellular response in periprosthetic tissue from non-loose implants.

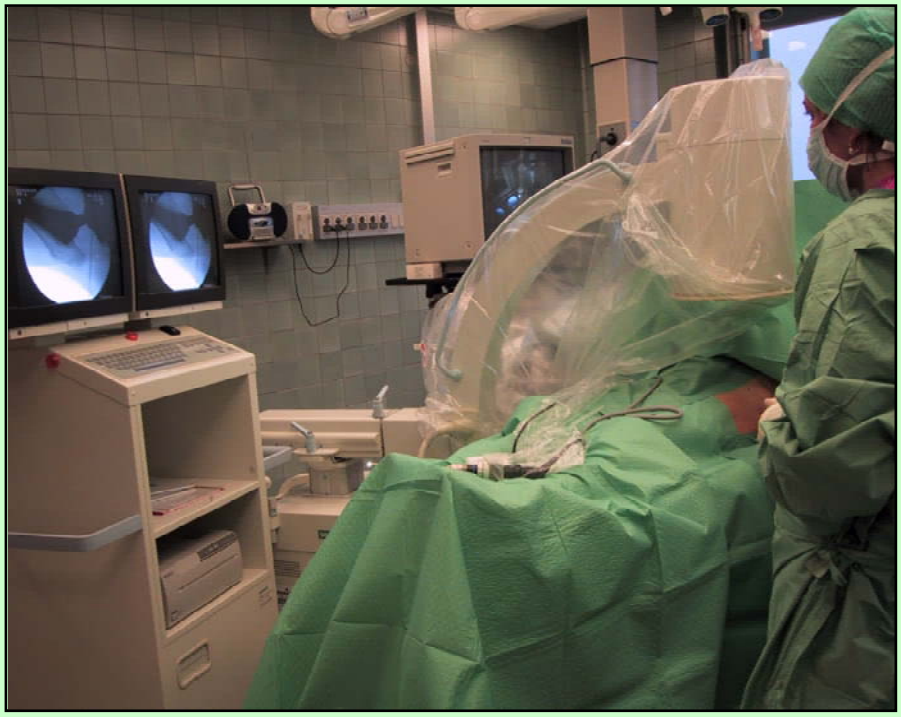


Fig. 6 illustrates the biopsy procedure guided by x-ray in the theatre.

2) Histomorphological preparation is described in the section “methods and patients” and Appendix C (Paper II). Potential bias prior to the evaluation is the tissue processing.

The estimate is affected by any dimensional change in the tissue. Shrinkage may not be identical in all types of tissue. Further, any section of the tissue deviating from the right angle to the profile may

influence the volume fraction estimated. The biopsy was freely rotated during processing hence the areas and profiles seen in the visual field of the light microscope were at random.

Though the method of preparation was optimised, thick sections is a known parameter to reduce penetration of antibodies. Additionally, some macrophages and endothelial cells may have expressed a very low amount of antigens below the detection limit. In both cases the volume fraction of the cells will be underestimated.

In four biopsies the morphology of the tissue was decomposed because of inadequate fixation. These biopsies were not evaluated. The results are further specified in Appendix C (Paper II).

3) The biopsy method only evaluated the tissue response through a “keyhole”. The observed tissue was roughly estimated to be 1/200 of the total surface of the pseudosynovial membrane, specified in Appendix C (Paper II).

The tissue response was evaluated by a point counting technique. Point counting is an unbiased estimate quantifying volume fraction of granuloma, macrophage, and endothelial cells in the pseudosynovial membrane [116-118]. Fig. 7. The technique is described in details in Appendix C (Paper II).

It was not clear whether the area observed was representative to the entire pseudosynovial membrane and a regional variance may occur. To evaluate the regional variance the volume fraction of granulomas in the pseudosynovial membrane was estimated from five different areas (i.e. different biopsies) within the same patient.

The coefficient of error was 66% and 143%, respectively. Although the local variation was high, it is most likely that the possibility to hit an area with a high or low volume fraction of granulomas would be the same.

The estimator variance also influence on the volume fraction estimated. An estimator variance test was performed to evaluate the variability of the observer and the equipment.

Double calculations were performed in the biopsies from six patients at two separate occasions. The patients chosen were randomised and selected by a computer. The results are presented in Table 2.

(a.) Volume fraction of granuloma

	n	Minimum	Maximum	Mean	Std. Error	SD	Variance
P1	2	0.03	0.07	0.050	0.020	0.028	0.001
P2	2	0.04	0.06	0.050	0.010	0.014	0
P3	2	0.02	0.03	0.025	0.005	0.007	0
P4	2	0.03	0.15	0.092	0.062	0.088	0.008
P5	2	0.04	0.14	0.090	0.050	0.070	0.005
P6	2	0	0	0	0	0	0

(b.) CD-68

	n	Minimum	Maximum	Mean	Std. Error	SD	Variance
P1	2	0.12	0.19	0.155	0.035	0.049	0.002
P2	2	0.01	0.01	0.010	0	0	0
P3	2	0.05	0.10	0.075	0.025	0.035	0.001
P4	2	0.06	0.09	0.075	0.015	0.021	0
P5	2	0.02	0.02	0.020	0	0	0
P6	2	0	0	0	0	0	0

(c.) CD-34

	n	Minimum	Maximum	Mean	Std. Error	SD	Variance
P1	2	0.03	0.05	0.040	0.010	0.014	0
P2	2	0	0	0	0	0.000	0
P3	2	0	0.01	0.003	0.002	0.003	0
P4	2	0.18	0.19	0.185	0.005	0.007	0
P5	2	0.04	0.10	0.070	0.030	0.042	0.002
P6	2	0.06	0.08	0.070	0.010	0.014	0

Table 2. Evaluation of the estimator variance the volume fraction of granuloma (a), CD-68 (b), and CD-34 (c) positive stained cells was calculated on two occasions in six randomised patients (P1-P6). The minimum, maximum, mean, std. error, SD, and variance were calculated.

The standard error was a little higher estimating the volume fraction of granuloma when compared macrophages and endothelial cells. The observer may redefine the margin of the granuloma different in two calculations.

Generally, each section should be endlessly thin to hit all profiles. Further, the area of the point gives a putative chance for overestimating the number of profiles. Optimally, the point should be endlessly small. For this reason the estimate of the volume fraction may deviate slightly.

A general grading system to quantify the cellular profiles and histopathological changes would be a helpful tool in the evaluation of biological responses. Future studies should carefully define the area from which the tissue is taken and in which clinical state the patient is in at the time of biopsy. This would facilitate comparison of the various studies.

To follow the pattern of the biological response to these three bearing materials, follow-up visits are important. The biological response may vary over time in the three groups. The results of the study provide an important baseline for the follow-up identification of parameters in predicting loosening.

Is quantification of chronic inflammatory cells and endothelial cells relevant in evaluating the host response to an implant? The quantification documents the presence and extent of chronic inflammatory cells in tissue close to an implant. The quantitative method does not evaluate the changes of the granulomas regarding cellular composition and appearance, on the size of the individual granuloma. Multiple small granulomas can result in the same volume fraction as few large granulomas.

Electron microscopy

This method provided the means to determine the ultrastructural localization of particles. Fig. 7. We did, however, not find particles in five patients with polyethylene bearings. This may be due to the fact that the electron density of polyethylene is similar to the embedding material [119]. Furthermore, polyethylene particles are transparent in TEM [73]. In four patients with alumina and one patient with CoCr bearings particles were not seen. The reason for this is most likely due to the fact that only a very small area was examined in the electron microscope and particles may have been localised outside the observed area as it has been shown by calculation from a mean annual volumetric wear rate that a person generates between 75.000-150.000 wear particles with each step taken with the arthroplasty [111].

The particles investigated in the thesis were relevant to evaluate since they were gradually produced *in vivo* and the particle dose response is relevant to future patients.

Counting of the particles was irrelevant since multiple particles were accumulated and the number of single particles was difficult to identify. This corresponds with the findings in Paper III, whereas the fabricated particles clearly demonstrated this accumulation. The fabricated particles were further used to determine the electron density of the *in vivo* produced particles for comparison.

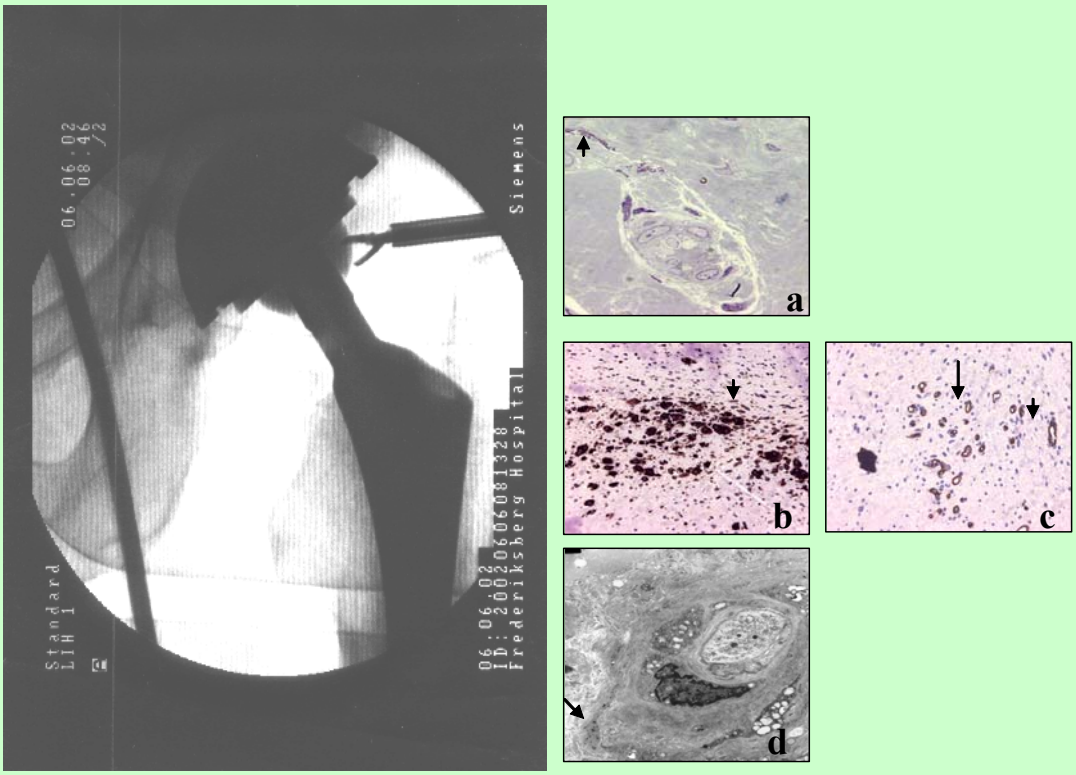


Fig. 7 illustrates the methods used for evaluation of the biopsies. a) histology (Toluidin blue). Arrow at particles b) immunohistochemestry (CD68 for macrophages - arrow), c) immunohistochemestry (CD34 for endothelial cells - arrow) d) TEM. Arrow at particles

RESULTS

Study I

Periprosthetic bone remodelling

The aim of the study was to examine the pattern of periprosthetic bone remodelling and compare the mean change in the periprosthetic BMD by bone density measurements (DEXA) using three different bearing combinations.

The study included 225 patients, and 188 patients (123 females, 65 males) were successfully scanned within one week and after one year. A number of 37 patients were excluded; specifications are given in Appendix C (Paper I). Clinically, all the patients had well-functioning hip implants.

The mean BMD measured after the operation was lower in the proximal zones compared to the distal zones. After one year, periprosthetic BMD decreased significantly in all Gruen zones in all three groups.

The loss in BMD was highest in the proximal zones: - 6.2% in the greater trochanter region (Gruen zone 1) and a – 12.7% in the lesser trochanter region (Gruen zone 7). In the other zones (Gruen 2-6) the mean BMD decrease was -5.3, -4.2, -2.1, -2.3, -5.6%, respectively.

The present study did not identify a significant difference in the periprosthetic mean BMD change within the first year after a total hip arthroplasty in any of the bearing material combinations: polyethylene-zirconia, CoCr-CoCr or alumina-alumina. Details are presented in Appendix C (Paper I).

Reproducibility is discussed in “Methodological considerations” and in Appendix C (Paper I).

Study II

Histomorphological study

The aim of the study was to examine the cellular response to three different bearing material combinations by estimating the volume fraction of macrophage, granuloma, and endothelial cells in the pseudosynovial membrane by point counting using light microscopy.

The study included biopsies of the pseudosynovial membrane of 37 patients. Granulomas were demonstrated in 33 of the 37 (35) biopsies. Two biopsies from the polyethylene-zirconia group were excluded because of failed preparation.

The median macrophage volume fractions for polyethylene-zirconia (n=15), CoCr-CoCr (n=9), and alumina-alumina (n=11) were 0.02, 0.04, and 0.004 respectively.

The median granuloma volume fractions for polyethylene-zirconia (n=13), CoCr-CoCr (n=9), and alumina-alumina (n=13), were 0.02, 0.04, and 0.02 respectively.

The median endothelial cell volume fractions for polyethylene-zirconia (n=15), CoCr-CoCr (n=9), and alumina-alumina (n=11) were 0.03, 0.02, and 0.05 respectively. 95 % of the cases had a volume fraction of granulomas within a range of 0.02-0.11.

After one year, the study did not identify any significant differences between the three groups with the different bearing material combinations. Further details are presented in Appendix C (Paper II).

Regional and estimator variance is specified in “Methodological considerations” and in Appendix C (Paper II).

Study III

Electron microscopy

The aim of the study was by transmission electron microscopy to examine the ultrastructural morphology of granuloma cells and particle localisation in the pseudosynovial membrane when using three different bearing material combinations.

A high number of particles were found in the pseudosynovial membrane of well functioning hip implants in all three groups as early as one year after the operation. The particles were observed both in the extracellular matrix and intracellularily in the cytoplasm of macrophages, fibroblasts, and endothelial cells in all groups.

The extracellular particles were located in the connective tissue between the collagen fibres. In the metal group extracellular particles were also seen as flake-like structures in the necrotic tissue from one patient. There were no inflammatory cells in relation to the extracellular particles.

The intracellular particles were located in the cytoplasm diffusely distributed or accumulated. In macrophages the particles were seen inside phagolysosomes.

Patients where no particles could be identified in the biopsy were found in all groups.

Mast cells were seen in few patients independent of bearing combination and glandular-like structures with a central lumen were observed in the alumina and the CoCr group. These cells were without secretion granula.

Fabricated particles

The particles found in the biopsies were comparable with the fabricated particles.

Details are presented in C (Paper III).

DISCUSSION

The biological response to the implants was evaluated by the following methods: 1) periprosthetic bone remodelling by DEXA, 2) estimation of volume fraction of macrophages, granulomas and endothelial cells by point counting, 3) early ultrastructural particle localisation by transmission electron microscopy

The biopsies in the present study gave the opportunity to study the first appearance of the pseudosynovial membrane and particles in non-loosened hip implants. The response of the pseudosynovial membrane to different wear materials of non-failed implants has not previously been evaluated.

The present studies could not demonstrate significant differences between the three groups one year after insertion of a hip implant using three different bearing material combinations.

The results can be discussed as follows:

1) Localisation of particles and cellular response
2) Cellular response
    - To different bearing materials
    - Individual host response
    - In loose and non-loose implants
3) Predictive parameters
4) Periprosthetic bone remodelling
5) What can be done to modify the biological response

Localisation of particles and cellular response

In all three groups a high number of particles were seen in the pseudosynovial membrane of well functioning hip implants one year after the operation.

The particles were observed in the extracellular matrix and intracellularily in macrophages, fibroblasts, and in endothelial cells in all three bearing material combinations. Thus particles were not found in all patients.

Regarding the extracellular particles, the questions are 1) why no inflammatory response was seen in relation to these particles? 2) what parameters can explain the extracellular localisation of these particles? The studies do not evaluate these questions. One suggestion is that these particles may differ morphologically or immunologically from the intracellular particles.

Bearing material combinations and cellular response

Previous studies *in vitro* and animal studies have demonstrated that the tissue reaction depended on specific types of foreign body materials [26,51,112,120,121,]. A prospective clinical study has to the authors knowledge not previously been made.

In the biopsies the volume fractions of granuloma from patients with implants were compared to patients with osteoarthritis during a primary hip arthroplasty. Granulomas were found in the prosthetic groups compared to the non-prosthetic group where no granulomas were found. These findings combined with the particles indicate a foreign body granulomatous inflammation.

Thus, the granulomatous inflammation found in the pseudosynovial membrane was independent of the bearing material combinations. There may be several explanations to this 1) the lymphatic or vascular transportation of particles away from the joint was high enough to prevent a high concentration and induce a more aggressive reaction as suggested by Willert et al [26]. In other words the patients examined in the present study may all have been below the threshold particle concentration to activate into a more aggressive response since the biopsies were taken only one year postoperative. It is likely that the cellular response may be more significant with time. 2) The biological response is the same to all bearing combinations. In line with this Lerouge et al. could retrospectively not demonstrate any difference in the cellular reaction when examining the interface membrane from loose ceramic-on-ceramic or metal-on-polyethylene hip arthroplasties (8.7 and 10.3 years implantation time) [55]. 3) The individual host response to the particles may be an important variable when evaluating the biological response. Specified below.

Individual host response

Each group had a case of very high volume fraction of granulomas. It is not clear whether these patients had a higher particle production compared to other patients. Clinically these patients were not extreme regarding activity level, age or weight compared to the major group with the exception of the patient with five dislocations. So far, we have not been able to explain this reaction.

It is likely that these patients are more sensitive to implants than others. If so the response in these patients may be independent of wear rate and wear type. Gene mapping of these patients in comparison with the others in this cohort may elucidate basic biological differences, and may thus enable us to identify potential fast rejecters. In the future PETscan may provide valuable information of the inflammatory response [122].

Cellular response in loose and non-loose implants

What specifies the granulomatous inflammation when comparing tissue from loose and non-loose implants?

The findings in the study imply that a granulomatous inflammation can be a common finding in non-loose implants. The granulomatous inflammation from non-loose implants was compared to tissue from aseptic loose hip implants described in previous studies [34]. These findings imply that the biological response is qualitatively similar in loose and non-loose implants, thus less aggressive in non-loose implants [34,114].

This suggests that the present study may reflect an early or a non-aggressive stage of the chronic granulomatous inflammation. It has been questioned whether there are two patterns of aseptic loosening, a slow and a fast (aggressive granulomatosis) [34]. Thus there may be distinctive factors accelerating the inflammation leading to early loosening.

These factors may not have been present in the cohort investigated by Bos *et al*. They semiquantified the biological response in the pseudosynovial membrane retrieved from well-fixated implants at autopsy [56]. The macrophage percentage in the synovial section was higher in the polyethylene-ceramic (mean 9 years) and polyethylene-CoCr (mean 9 years) group when compared to the ceramic-ceramic (mean 8 years) group. The macrophage percentage was between 20-40% and to

40-60 % and necrosis was seen. The histological findings were qualitatively similar to the present study, although more extended. The findings were comparable to those in loose implants. The question is why these implants were well fixated despite the high quantity of macrophages with intracellular particles and necrosis in the periprosthetic tissue? Bos have previously compared a more extended biological reaction to the implantation time [32].

Fibroblasts have been suggested to be involved when the granulomatous inflammation is progressing to an aggressive granulomatosis [34,77]. The theories have been ranging from uncoupling of the fibroblasts in the bone remodelling to a synergistic effect of the fibroblasts activation of the macrophage. The role of the macrophage is not clear.

Whereas the macrophage has been extensively investigated, the putative role of endothelial cells in aseptic loosening has not been discussed. Endothelial cells with intracellular particles have not previously been described in tissue from both loose and non-loose hip implants and independent of bearing material combination. The role of these cells in the inflammatory process and aseptic loosening is not clear. Perhaps a different production of cell mediators as a response to different particle types could influence the periprosthetic bone remodelling. There is, however, not much doubt that the endothelial cells have a role in the periprosthetic inflammation.

The exactly role of the different cells in the biological response to an implant is complex and not known in details.

Predictive parameters

Although the pattern of the granulomatous inflammation is qualitatively similar in aseptic loose and well-fixated implants there may be different stages in the response possible to quantify.

To reduce the rate of aggressive chronic inflammation and early aseptic loosening an understanding of the immunological response to the implant is necessary. What parameters trigger the chronic inflammation into a more aggressive state? Why does the onset of bone resorption occur at different speed in two patients with the same prosthesis? How is the patient at risk of early loosening identified? What are the most reliable predicting factors?

A method of quantification was used in the study and the volume fraction of granulomas in the pseudosynovial membrane of well-functioning hip implants was estimated [114].

Ninety five percent of the cases had a volume fraction of granulomas within a range of 0.03-0.06 [114]. The pseudosynovial membrane was compared with non-prosthetic controls and granulomas were solely demonstrated in the prosthetic group and not to the non-prosthetic group [114].

Particles were not quantified in this study, but the severity of the granulomatous response and area of microvasculature has previously been demonstrated to correlate with the degree of periprosthetic bone resorption and wear debris [64,85]. It was not possible from the parameters quantified at this early stage to predict the future periprosthetic cellular cascade and the potential cases of early aseptic loosening. The long-term response must be observed and related to the present observations.

A non-invasive method for evaluating the particle accumulation in the periprosthetic tissue is not present. With a non-invasive method, it would be possible to correlate the local concentration of particles with the biological response in a longitudinal study. At present, it is only possible to examine the *in vivo* produced particles and the periprosthetic tissue at time of revision or by a biopsy. Therefore, a correlation of the granulomatous inflammation, the concentration of particles, and the periprosthetic bone remodelling are difficult to evaluate. Provided the particles have influenced the bone remodelling in the present study there were no difference when comparing the three bearing material combinations.

It would also be interesting to discus which parameters are relevant in evaluating the biocompability. It may be relevant to demonstrate an active recognition of positive signals instead of inertness. Therefore, it is relevant to define which parameters are significant. It is thus important to develop new tests for evaluating the biocompability of the biomaterials used. There will not be one single test method because the reactions are numerous and complex [123].

Periprosthetic bone remodelling

Several parameters previously mentioned influence the periprosthetic bone remodelling, but do not completely explain why some patients develop an aggressive periprosthetic osteolysis.

A granulomatous inflammation was seen in the pseudosynovial membrane and a periprosthetic bone resorption was measured. To what extent the particles have contributed to the periprosthetic bone

resorption in the early phase after surgery is not known. It is possible that various parameters known to influence bone remodelling may have camouflaged a very small influence of the particles. A difference below the detectable limit of methods used is probably not clinically relevant.

DEXA is a valuable method to evaluate the local bone response to the implant but the method do not determine to what extent each variable parameter has contributed to the bone remodelling. Several variables may have contributed, such as stress shielding, method of surgery, host factor, particle induced foreign body response, and vascular injury as mentioned previously. It is most likely that the bone resorption measured was a combination of all these factors. Hence, the present study used identical implants and method of surgery in the three groups in order to examine the influence of the bearing materials.

What can be done to modify the biological response

There has been a general tendency to prefer inert materials for implants [123]. The idea has been that an inert material will be better tolerated by the body. However, Williams interestingly suggested that this tolerance may be equal to a passive ignorance rather than an active recognition [123]. The material may not be incorporated if ignored. As alternative he suggests materials inducing benign tolerance [123]. In such case materials that can induce bone formation are favoured to inert materials.

There have been some initiatives to stimulate bone formation. Hydroxyapatite coating has been introduced to improve fixation of the stem. Hydroxyapatite is composed of calcium phosphate and is incorporated into bone as a physiological mineral. The aim of this coating is to increase the osteointegration between bone and implant.

Hydroxyapatite coated implants coated with growth factors (TGF-β) have proved to increase bone osteointegration to the implant with one third, but did not increase bone volume or mechanical strength when compared to control animals [124]. Migration of implants coated with hydroxyapatite were in a clinical study reduced after one year when compared to non-coated controls and it has also been shown that hydroxyapatite inhibits migration of polyethylene particles [125].

CONCLUSION

Regardless of bearing material combination, the pseudosynovial membrane contained no significant differences in volume fraction of granulomas, macrophages, and endothelial cells one year after implantation.

Extra- and intracellular particles were not correlated to type of bearing regarding granuloma cells, fibroblasts, and endothelial cells.

There was no difference between groups with different bearing materials regarding change in BMD one year after surgery.

Since the early biological response in the pseudosynovial membrane of well functioning hip implants have similarities with periprosthetic tissue from revised hip implants and similarities between the three groups, the author suggests that the mechanism of failure may be the same independent of the bearing material materials.

At this initial stage after hip surgery, the present studies did not provide evidence for different types of bearing materials having significant impact on bone remodelling adjacent to cemented hip arthroplasties within the first year after surgery.

FUTURE PERSPECTIVES

The present study did not reveal significant differences in the biological response to the three different bearings in 37 patients one year after hip implantation.

The observations, however, contribute a comprehensive series of results that may prove valuable in the on-going follow-up studies of our cohort of patients.

It may very well be that loosening of hip implants is independent of bearing components. Aseptic loosening is likely to be an individual reaction, i.e. individual aggressive response to the implant.

How do aggressive responders differ from those who sustain with their hip implants? The answer to this question could well be provided by gene mapping of aggressive responders and compare their genetic profile with those who sustain.

The genetic analyses should emphasize on differences in inflammatory responses focusing on the cellular participants in the reaction i.e. monocytes/macrophages, fibroblasts and endothelial cells and their production of cytokines. Identification of molecules that play major roles in the loosening opens the possibility of modulation or hindering of the bone destruction adjacent to the implant.

If or when modulation of the bone destruction becomes feasible it is of paramount importance to be able to identify the very early detrimental changes in the pertinent area around the implant. A very recent study provided a means of non-invasive examination of the biological activities in the periprosthetic tissue, namely PET scanning [122].

SUMMARY

World wide, approximately 1 million hip arthroplasties are implanted every year. The cumulated rate of revision is annually about 1 % (approximately 10% of these prostheses will be revised after 10 years) and is most often a result of implant loosening. The loosening is often aseptic and the condition is a well-known limit for a long-term survival of the implant. Wear particles derived from the articulating materials of the implant are an accepted cause of aseptic loosening.

The accumulated wear particles attract white blood cells, especially monocytes/macrophages that can phagocytize the non-digestible wear particles. In some occasions, the macrophages with intracellular non-digestible wear particles accumulate into foreign body granulomas or giant cells. The giant cells can be found in revision tissue of failed implants and have common morphological and biological features with osteoclasts, cells that are specialised in bone resorption.

The number of macrophages is positively correlated to the number of polyethylene particles in the periprosthetic tissue and the degree of bone resorption is correlated to the degree of granulomatous inflammation.

This correlation between wear particles and implant loosening has contributed to the wish for more wear resistant alternatives to the conventional polyethylene-metal bearings. These bearings are most often ceramic-ceramic (alumina) or metal-metal (CoCr) or polyethylene-ceramic (zirconia).

A reduced wear rate or a different biological response of these bearing materials may influence the formerly described cellular response and thus the bone resorption around the implant. The goal is to reduce the rate of revision in the future.

The aim of the present phd thesis was to investigate if there was a difference in the biological response between three groups with identical hip implants except from the bearing materials: polyethylene-ceramics (zirconia), metal-metal (CoCr), or ceramic-ceramic (alumina).

A total two hundred and twenty five patients were included. Prior to the operation, the patients were randomised into one of the three groups.

After the operation, the periprosthetic bone mineral density was measured by DEXA (bone mineral density). The procedure was repeated after one year, and the change in bone mineral density was calculated and compared within the groups.

After one year, biopsies were taken from the pseudosynovial membrane in 37 volunteers (of the 225 patients) and examined as follows.

1. Biopsies were evaluated in which the volume fraction of macrophages, granulomas, and endothelial cells was quantified by light microscopy.
2. Biopsies were evaluated by the transmission electron microscope to describe the ultrastructural morphology of the cells and the localisation of the particles in pseudosynovial membrane.
3. Biopsies were used for quantification of cytokines in the pseudosynovial membrane by flow cytometry and ELISA.

The results showed no significant differences in mean change of BMD, volume fraction of macrophages, granulomas, and endothelial cells or the ultrastructural localisation of wear particles between the three groups with the three different bearing combinations. The cytokine study is not yet finished.

RESUMÉ PÅ DANSK

På verdensplan indsættes årligt omkring 1 million primære hoftealloplastikker. Den kumulerede udskiftningsrate for disse proteser er omkring 1 % årligt (omkring 10 % af disse proteser vil blive udskiftet i løbet af 10 år). Årsagen er oftest en aseptisk betinget og tilstanden er en velkendt begrænsning til hofteprotesers langtidsoverlevelse. Slidpartikler fra protesens egne slidflader er en accepteret årsag til den aseptiske proteseløsning.

De akkumulerede slidpartikler tildrager hvide blodlegemer, specielt monocyt/makrofager, der fagocyterer (optager) disse ikke nedbrydelige partikler. I nogle tilfælde danner makrofager med intracellulære slidpartikler granulomer (en hob af makrofager) eller kæmpeceller. Kæmpeceller kan findes i vævet omkring løse proteser og har morfologiske og biologiske egenskaber der minder om osteoklaster, celler specialiseret i knoglenedbrydning. Antallet af makrofager er positivt korreleret til antallet af polyethylenpartikler i vævet omkring protesen og knoglenedbrydningen er korreleret til graden af den granulomatøse inflammation.

Denne sammenhæng mellem slidpartikler og proteseløsning har medført et ønske om stærkere slidfladematerialer som alternativ til den konventionelle polyethylen – metal kombination. Disse slidmaterialer er oftest keramik-keramik (alumina), metal-metal (CoCr) eller polyethylen-keramik (alumina eller zirconia).

En reduceret slidrate eller varierende biologisk respons for disse materialer kan have betydning for den tidligere beskrevne cellulære respons og hermed knoglenedbrydningen omkring protesen. Målet er at reducerer antallet af revisioner i fremtiden.

Formålet med phd studiet var at undersøge, hvorvidt der efter et år var forskel på vævsreaktionen hos tre grupper af patienter med identiske hofteimplantater undtaget slidfladematerialerne: polyethylen – keramik (zirconia), metal - metal (CoCr) eller keramik – keramik (alumina).

I alt tohundrede og femogtyve 225 patienter indgik i studiet. Forud for operationen blev patienterne randomiseret til en af de tre gruppe.

Efter operationen blev knoglemineraltætheden omkring protesen målt ved DEXA (knogletæthedsmåling). Proceduren blev gentaget efter et år og ændringer i knoglemineraltætheden blev beregnet og sammenlignet for de respektive grupper.

Efter et år blev der udtaget vævsprøver fra pseudosynovial membranen på 37 frivillige (af de 225 patienter) og undersøgt for følgende:

1. Biopsierne blev evalueret og volumenfraktion af makrofager, granulomer og endotelceller blev kvantiteret i lysmikroskop.
2. Biopsierne blev evalueret ved transmission elektron mikroskop og den ultrastrukturelle morfologi og partikellokalisation i pseudosynovial membranen blev beskrevet.
3. Biopsier blev benyttet til kvatitering af cytokiner i pseudosynovial membranen ved flow cytometri og ELISA.

Resultaterne ikke nogen signifikant forskel på knogletætheden omkring protesen, volumenfraktion af makrofager, granulomer og endotelceller eller den ultrastrukturelle morfologi for de tre grupper med forskellige slidflader. Cytokinstudiet er ikke færdigt.

REFERENCES

1. Hoaglund FT, Steinbach LS. Primary osteoarthritis of the hip: etiology and epidemiology. *J Am Acad Orthop Surg* 2001; **9**: 320-7.

2. Sneppen O, Soballe K. [Alloplasty. Development of well-functioning and durable joint implant-- a biomechanical and biological challenge]. *Ugeskr Laeger* 2000; **162**: 64-5.

3. Clarke IC, Good V, Anissian L, Gustafson A. Charnley wear model for validation of hip simulators--ball diameter versus polytetrafluoroethylene and polyethylene wear. *Proc Inst Mech Eng [H]* 1997; **211**: 25-36.

4. Charnley J. Arthroplasty of the hip. A new operation. *Lancet* 1961; **1**: 1129-32.

5. The classic: Arthroplasty of the hip: a new operation by John Charnley, M.B., B. Sc. Manc., F.R.C.S. Reprinted from Lancet pp. 1129-32, 196l. *Clin Orthop* 1973; **95**: 4-8.

6. Haboush EJ. A new operation for arthroplasty of the hip based on biomechanics, photoelasticity, fast-setting dental acrylic, and other considerations. 1953 [classicle article]. *Bull Hosp Jt Dis* 1996; **55**: 95-111.

7. McKee GK, Watson-Farrar J. Replacement of arthritic hips by the McKee-Farrar prosthesis. *J Bone Joint Surg Br* 1966; **48**: 245-59.

8. Sivash KM. The development of a total metal prosthesis for the hip joint from a partial joint replacement. *Reconstr Surg Traumatol* 1969; **11**: 53-62.

9. Amstutz HC, Grigoris P. Metal on metal bearings in hip arthroplasty. *Clin Orthop* 1996; **329 Suppl**: S11-S34.

10. O'Boyle CA, McGee H, Hickey A, O'Malley K, Joyce CR. Individual quality of life in patients undergoing hip replacement. *Lancet* 1992; **339**: 1088-91.

11. Laupacis A et al. The effect of elective total hip replacement on health-related quality of life. *J Bone Joint Surg Am* 1993; **75**: 1619-26.

12. Lucht U, Johnsen SP. *The Danish Hip Arthroplasty Register*.: 2004.

13. Lucht U. The Danish Hip Arthroplasty Register. *Acta Orthop Scand* 2000; **71**: 433-9.

14. Herberts P, Malchau H. Long-term registration has improved the quality of hip replacement: a review of the Swedish THR Register comparing 160,000 cases. *Acta Orthop Scand* 2000; **71**: 111-21.

15. Malchau H, Herberts P, Ahnfelt L. Prognosis of total hip replacement in Sweden. Follow-up of 92,675 operations performed 1978-1990. *Acta Orthop Scand* 1993; **64**: 497-506.

16. Havelin LI et al. The Norwegian Arthroplasty Register: 11 years and 73,000 arthroplasties. *Acta Orthop Scand* 2000; **71**: 337-53.

17. Havelin LI. The Norwegian Joint Registry. *Bull Hosp Jt Dis* 1999; **58**: 139-47.

18. Pedersen A et al. Registration in the danish hip arthroplasty registry: completeness of total hip arthroplasties and positive predictive value of registered diagnosis and postoperative complications. *Acta Orthop Scand* 2004; **75**: 434-41.

19. Peter Herberts, Henrik Malchau, Göran Garellick. *The Swedish National Hip Arthroplasty Register - Annual Report.*: 2003.

20. Sharp DJ, Porter KM. The Charnley total hip arthroplasty in patients under age 40. *Clin Orthop* 1985; **201**: 51-6.

21. Sochart DH, Porter ML. The long-term results of Charnley low-friction arthroplasty in young patients who have congenital dislocation, degenerative osteoarthrosis, or rheumatoid arthritis. *J Bone Joint Surg Am* 1997; **79**: 1599-617.

22. White SH. The fate of cemented total hip arthroplasty in young patients. *Clin Orthop* 1988; **231**: 29-34.

23. Charnley J, Follacci FM, Hammond BT. The long-term reaction of bone to self-curing acrylic cement. *J Bone Joint Surg Br* 1968; **50**: 822-9.

24. Charnley J. Fracture of femoral prostheses in total hip replacement. A clinical study. *Clin Orthop* 1975; **111**: 105-20.

25. 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**: 612-8.

26. Willert HG. Reactions of the articular capsule to wear products of artificial joint prostheses. *J Biomed Mater Res* 1977; **11**: 157-64.

27. Goldring SR et al. The synovial-like membrane at the bone-cement interface in loose total hip replacements and its proposed role in bone lysis. *J Bone Joint Surg Am* 1983; **65**: 575-84.

28. Jasty MJ, Floyd WE, III, Schiller AL, Goldring SR, Harris WH. Localized osteolysis in stable, non-septic total hip replacement. *J Bone Joint Surg Am* 1986; **68**: 912-9.

29. Jones LC, Hungerford DS. Cement disease. *Clin Orthop* 1987; **225**: 192-206.

30. Korovessis P, Repanti M. Evolution of aggressive granulomatous periprosthetic lesions in cemented hip arthroplasties. *Clin Orthop* 1994; **300**: 155-61.

31. Konttinen Y et al. Cytokines in aseptic loosening of total hip replacement. *Current Orthopaedics* 1997; **11**: 40-7.

32. Bos I. [Tissue reactions around loosened hip joint endoprostheses. A histological study of secondary capsules and interface membranes]. *Orthopade* 2001; **30**: 881-9.

33. Boynton EL, Henry M, Morton J, Waddell JP. The inflammatory response to particulate wear debris in total hip arthroplasty. *Can J Surg* 1995; **38**: 507-15.

34. Santavirta S et al. Aggressive granulomatous lesions associated with hip arthroplasty. Immunopathological studies. *J Bone Joint Surg Am* 1990; **72**: 252-8.

35. Santavirta S et al. Aggressive granulomatous lesions in cementless total hip arthroplasty. *J Bone Joint Surg Br* 1990; **72**: 980-4.

36. Santavirta S et al. Alternative materials to improve total hip replacement tribology. *Acta Orthop Scand* 2003; **74**: 380-8.

37. Santavirta S, Nordstrom D, Metsarinne K, Konttinen YT. Biocompatibility of polyethylene and host response to loosening of cementless total hip replacement. *Clin Orthop* 1993; **297**: 100-10.

38. Urban RM, Jacobs JJ, Gilbert JL, Galante JO. Migration of corrosion products from modular hip prostheses. Particle microanalysis and histopathological findings. *J Bone Joint Surg Am* 1994; **76**: 1345-59.

39. Aspenberg P, Van d, V. Migration, particles, and fluid pressure. A discussion of causes of prosthetic loosening. *Clin Orthop* 1998; **352**: 75-80.

40. Urban RM et al. Dissemination of wear particles to the liver, spleen, and abdominal lymph nodes of patients with hip or knee replacement. *J Bone Joint Surg Am* 2000; **82**: 457-76.

41. Santavirta S et al. Activation of periprosthetic connective tissue in aseptic loosening of total hip replacements. *Clin Orthop* 1998; **352**: 16-24.

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

43. Wirta J et al. Revision of aggressive granulomatous lesions in hip arthroplasty. *J Arthroplasty* 1990; **5 Suppl**: S47-S52.

44. Archibeck MJ, Jacobs JJ, Black J. Alternate bearing surfaces in total joint arthroplasty: biologic considerations. *Clin Orthop* 2000; **379**: 12-21.

45. Doorn PF, Campbell PA, Amstutz HC. Metal versus polyethylene wear particles in total hip replacements. A review. *Clin Orthop* 1996; **329 Suppl**: S206-S216.

46. Goodman SB. Does the immune system play a role in loosening and osteolysis of total joint replacements? *J Long Term Eff Med Implants* 1996; **6**: 91-101.

47. Jacobs JJ, Roebuck KA, Archibeck M, Hallab NJ, Glant TT. Osteolysis: basic science. *Clin Orthop* 2001; **393**: 71-7.

48. Jazrawi LM, Kummer FJ, DiCesare PE. Alternative bearing surfaces for total joint arthroplasty. *J Am Acad Orthop Surg* 1998; **6**: 198-203.

49. Shanbhag AS, Jacobs JJ, Black J, Galante JO, Glant TT. Macrophage/particle interactions: effect of size, composition and surface area. *J Biomed Mater Res* 1994; **28**: 81-90.

50. Doorn PF, Mirra JM, Campbell PA, Amstutz HC. Tissue reaction to metal on metal total hip prostheses. *Clin Orthop* 1996; **329 Suppl**: S187-S205.

51. Gelb H, Schumacher HR, Cuckler J, Ducheyne P, Baker DG. In vivo inflammatory response to polymethylmethacrylate particulate debris: effect of size, morphology, and surface area. *J Orthop Res* 1994; **12**: 83-92.

52. Vermes C et al. The effects of particulate wear debris, cytokines, and growth factors on the functions of MG-63 osteoblasts. *J Bone Joint Surg Am* 2001; **83-A**: 201-11.

53. Willert HG, Bertram H, Buchhorn GH. Osteolysis in alloarthroplasty of the hip. The role of ultra-high molecular weight polyethylene wear particles. *Clin Orthop* 1990; **258**: 95-107.

54. Yoon TR, Rowe SM, Jung ST, Seon KJ, Maloney WJ. Osteolysis in association with a total hip arthroplasty with ceramic bearing surfaces. *J Bone Joint Surg Am* 1998; **80**: 1459-68.

55. Lerouge S, Huk O, Yahia L, Witvoet J, Sedel L. Ceramic-ceramic and metal-polyethylene total hip replacements: comparison of pseudomembranes after loosening. *J Bone Joint Surg Br* 1997; **79**: 135-9.

56. Bos I, Willmann G. Morphologic characteristics of periprosthetic tissues from hip prostheses with ceramic-ceramic couples: a comparative histologic investigation of 18 revision and 30 autopsy cases. *Acta Orthop Scand* 2001; **72**: 335-42.

57. Mochida Y, Boehler M, Salzer M, Bauer TW. Debris from failed ceramic-on-ceramic and ceramic-on-polyethylene hip prostheses. *Clin Orthop* 2001; **389**: 113-25.

58. Hatton A et al. Alumina-alumina artificial hip joints. Part I: a histological analysis and characterisation of wear debris by laser capture microdissection of tissues retrieved at revision. *Biomaterials* 2002; **23**: 3429-40.

59. Christel PS. Biocompatibility of surgical-grade dense polycrystalline alumina. *Clin Orthop* 1992; **282**: 10-8.

60. Amstutz HC, Campbell P, Kossovsky N, Clarke IC. Mechanism and clinical significance of wear debris-induced osteolysis. *Clin Orthop* 1992; **276**: 7-18.

61. Cotran RS, Kumar V, Collins T. *Robbins pathologic basis of disease.*: 1999.

62. Chambers TJ, Spector WG. Inflammatory giant cells. *Immunobiology* 1982; **161**: 283-9.

63. James DG. A clinicopathological classification of granulomatous disorders. *Postgrad Med J* 2000; **76**: 457-65.

64. Jasty M et al. Etiology of osteolysis around porous-coated cementless total hip arthroplasties. *Clin Orthop* 1994; **308**: 111-26.

65. Athanasou NA, Quinn J, Bulstrode CJ. Resorption of bone by inflammatory cells derived from the joint capsule of hip arthroplasties. *J Bone Joint Surg Br* 1992; **74**: 57-62.

66. Athanasou NA, Sabokbar A. Human osteoclast ontogeny and pathological bone resorption. *Histol Histopathol* 1999; **14**: 635-47.

67. Fujikawa Y, Sabokbar A, Neale S, Athanasou NA. Human osteoclast formation and bone resorption by monocytes and synovial macrophages in rheumatoid arthritis. *Ann Rheum Dis* 1996; **55**: 816-22.

68. Fujikawa Y, Quinn JM, Sabokbar A, McGee JO, Athanasou NA. The human osteoclast precursor circulates in the monocyte fraction. *Endocrinology* 1996; **137**: 4058-60.

69. Athanasou NA et al. An immunohistological study of giant-cell tumour of bone: evidence for an osteoclast origin of the giant cells. *J Pathol* 1985; **147**: 153-8.

70. Revell PA. Synovial lining cells. *Rheumatol Int* 1989; **9**: 49-51.

71. Ohlin A, Kindblom LG. The ultrastructure of the tissue surrounding the Christiansen total hip. *Acta Orthop Scand* 1988; **59**: 629-34.

72. Bentley SA, Tralka TS, Alabaster O. Phagocytic properties of bone marrow fibrobalsts. *Exp Hematol* 1981; **9**: 318.

73. Pazzaglia UE, Dell'Orbo C, Wilkinson MJ. The foreign body reaction in total hip arthroplasties. A correlated light-microscopy, SEM, and TEM study. *Arch Orthop Trauma Surg* 1987; **106**: 209-19.

74. Bauer TW. Particles and periimplant bone resorption. *Clin Orthop* 2002; **405**: 138-43.

75. Pap T et al. Osteoclast-independent bone resorption by fibroblast-like cells. *Arthritis Res Ther* 2003; **5**: R163-R173.

76. Manlapaz M, Maloney WJ, Smith RL. In vitro activation of human fibroblasts by retrieved titanium alloy wear debris. *J Orthop Res* 1996; **14**: 465-72.

77. Lind M, Trindade MC, Yaszay B, Goodman SB, Smith RL. Effects of particulate debris on macrophage-dependent fibroblast stimulation in coculture. *J Bone Joint Surg Br* 1998; **80**: 924-30.

78. Waris V et al. Basic fibroblast growth factor (bFGF) in the synovial-like membrane around loose total hip prostheses. *Scand J Rheumatol* 1996; **25**: 257-62.

79. Sakai H et al. Fibroblasts from the inner granulation tissue of the pseudocapsule in hips at revision arthroplasty induce osteoclast differentiation, as do stromal cells. *Ann Rheum Dis* 2002; **61**: 103-9.

80. Quinn JM, Horwood NJ, Elliott J, Gillespie MT, Martin TJ. Fibroblastic stromal cells express receptor activator of NF-kappa B ligand and support osteoclast differentiation. *J Bone Miner Res* 2000; **15**: 1459-66.

81. Ziats NP, Miller KM, Anderson JM. In vitro and in vivo interactions of cells with biomaterials. *Biomaterials* 1988; **9**: 5-13.

82. Mandelin J et al. Imbalance of RANKL/RANK/OPG system in interface tissue in loosening of total hip replacement. *J Bone Joint Surg Br* 2003; **85**: 1196-201.

83. Collin-Osdoby P et al. Receptor activator of NF-kappa B and osteoprotegerin expression by human microvascular endothelial cells, regulation by inflammatory cytokines, and role in human osteoclastogenesis. *J Biol Chem* 2001; **276**: 20659-72.

84. McGowan NW, Walker EJ, Macpherson H, Ralston SH, Helfrich MH. Cytokine-activated endothelium recruits osteoclast precursors. *Endocrinology* 2001; **142**: 1678-81.

85. Jell GM, Al Saffar N. Does a pro-angiogenic state exist in the bone-implant interface of aseptically loosened joint prosthesis? *J Mater Sci Mater Med* 2001; **12**: 1069-73.

86. Miyanishi K et al. Periprosthetic osteolysis: induction of vascular endothelial growth factor from human monocyte/macrophages by orthopaedic biomaterial particles. *J Bone Miner Res* 2003; **18**: 1573-83.

87. Adler CP, Reichelt A. Haemangiosarcoma of bone. *Int Orthop* 1985; **8**: 273-9.

88. Green TR, Fisher J, Stone M, Wroblewski BM, Ingham E. Polyethylene particles of a 'critical size' are necessary for the induction of cytokines by macrophages in vitro. *Biomaterials* 1998; **19**: 2297-302.

89. Sieving A, Wu B, Mayton L, Nasser S, Wooley PH. Morphological characteristics of total joint arthroplasty-derived ultra-high molecular weight polyethylene (UHMWPE) wear debris that provoke inflammation in a murine model of inflammation. *J Biomed Mater Res* 2003; **64A**: 457-64.

90. Yang SY et al. Diverse cellular and apoptotic responses to variant shapes of UHMWPE particles in a murine model of inflammation. *Biomaterials* 2002; **23**: 3535-43.

91. Schmalzried TP, Jasty M, Harris WH. Periprosthetic bone loss in total hip arthroplasty. Polyethylene wear debris and the concept of the effective joint space. *J Bone Joint Surg Am* 1992; **74**: 849-63.

92. Dowd JE, Sychterz CJ, Young AM, Engh CA. Characterization of long-term femoral-head-penetration rates. Association with and prediction of osteolysis. *J Bone Joint Surg Am* 2000; **82-A**: 1102-7.

93. Livermore J, Ilstrup D, Morrey B. Effect of femoral head size on wear of the polyethylene acetabular component. *J Bone Joint Surg Am* 1990; **72**: 518-28.

94. Catelas I et al. Flow cytometric analysis of macrophage response to ceramic and polyethylene particles: effects of size, concentration, and composition. *J Biomed Mater Res* 1998; **41**: 600-7.

95. Maloney WJ, Smith RL, Castro F, Schurman DJ. Fibroblast response to metallic debris in vitro. Enzyme induction cell proliferation, and toxicity. *J Bone Joint Surg Am* 1993; **75**: 835-44.

96. Oh I, Harris WH. Proximal strain distribution in the loaded femur. An in vitro comparison of the distributions in the intact femur and after insertion of different hip-replacement femoral components. *J Bone Joint Surg Am* 1978; **60**: 75-85.

97. Frost HM. A 2003 update of bone physiology and Wolff's Law for clinicians. *Angle Orthod* 2004; **74**: 3-15.

98. Zahiri CA et al. Lessons learned from loosening of the McKee-Farrar metal-on-metal total hip replacement. *J Arthroplasty* 1999; **14**: 326-32.

99. elMaraghy AW, Schemitsch EH, Waddell JP. Greater trochanteric blood flow during total hip arthroplasty using a posterior approach. *Clin Orthop* 1999; **363**: 151-7.

100. Hupel TM, Schemitsch EH, Aksenov SA, Waddell JP. Blood flow changes to the proximal femur during total hip arthroplasty. *Can J Surg* 2000; **43**: 359-64.

101. Santavirta S et al. Periprosthetic microvasculature in loosening of total hip replacement. *Arch Orthop Trauma Surg* 1996; **115**: 286-9.

102. Bi Y et al. Adherent endotoxin on orthopedic wear particles stimulates cytokine production and osteoclast differentiation. *J Bone Miner Res* 2001; **16**: 2082-91.

103. Skoglund B, Larsson L, Aspenberg PA. Bone-resorptive effects of endotoxin-contaminated high-density polyethylene particles spontaneously eliminated in vivo. *J Bone Joint Surg Br* 2002; **84**: 767-73.

104. Hallab N, Merritt K, Jacobs JJ. Metal sensitivity in patients with orthopaedic implants. *J Bone Joint Surg Am* 2001; **83-A**: 428-36.

105. Willmann G. Ceramics for total hip replacement--what a surgeon should know. *Orthopedics* 1998; **21**: 173-7.

106. Willmann G. The evolution of ceramics in total hip replacement. *Hip International* 2000; **10**: 193-203.

107. Semlitsch M, Willert HG. Clinical wear behaviour of ultra-high molecular weight polyethylene cups paired with metal and ceramic ball heads in comparison to metal-on- metal pairings of hip joint replacements. *Proc Inst Mech Eng [H]* 1997; **211**: 73-88.

108. Saikko V, Calonius O, Keranen J. Wear of conventional and cross-linked ultra-high-molecular-weight polyethylene acetabular cups against polished and roughened CoCr femoral heads in a biaxial hip simulator. *J Biomed Mater Res* 2002; **63**: 848-53.

109. Affatato S, Frigo M, Toni A. An in vitro investigation of diamond-like carbon as a femoral head coating. *J Biomed Mater Res* 2000; **53**: 221-6.

110. Aspenberg P et al. Benign response to particles of diamond and SiC: bone chamber studies of new joint replacement coating materials in rabbits. *Biomaterials* 1996; **17**: 807-12.

111. Dowson D. New joints for the Millennium: wear control in total replacement hip joints. *Proc Inst Mech Eng [H]* 2001; **215**: 335-58.

112. Green TR, Fisher J, Matthews JB, Stone MH, Ingham E. Effect of size and dose on bone resorption activity of macrophages by in vitro clinically relevant ultra high molecular weight polyethylene particles. *J Biomed Mater Res* 2000; **53**: 490-7.

113. Gruen TA, McNeice GM, Amstutz HC. "Modes of failure" of cemented stem-type femoral components: a radiographic analysis of loosening. *Clin Orthop* 1979; **141**: 17-27.

114. Nygaard M, Elling F, Bastholm L, Søballe K, Borgwardt A. Early cellular response of the pseudosynovial membrane after a total hip arthroplasty using three different bearing surface materials. A randomised prospective study. *Submitted* 2004.

115. Finsen V, Anda S. Accuracy of visually estimated bone mineralization in routine radiographs of the lower extremity. *Skeletal Radiol* 1988; **17**: 270-5.

116. Gundersen HJ et al. Some new, simple and efficient stereological methods and their use in pathological research and diagnosis. *APMIS* 1988; **96**: 379-94.

117. Coggeshall RE, Lekan HA. Methods for determining numbers of cells and synapses: a case for more uniform standards of review. *J Comp Neurol* 1996; **364**: 6-15.

118. Larsen JO. Stereology of nerve cross sections. *J Neurosci Methods* 1998; **85**: 107-18.

119. Benz EB et al. Transmission electron microscopy of intracellular particles of polyethylene from joint replacement prostheses: size distribution and cellular response. *Biomaterials* 2001; **22**: 2835-42.

120. Goodman SB, Fornasier VL, Lee J, Kei J. The histological effects of the implantation of different sizes of polyethylene particles in the rabbit tibia. *J Biomed Mater Res* 1990; **24**: 517-24.

121. Haynes DR, Boyle SJ, Rogers SD, Howie DW, Vernon-Roberts B. Variation in cytokines induced by particles from different prosthetic materials. *Clin Orthop* 1998; **352**: 223-30.

122. Sorensen J, Ullmark G, Langstrom B, Nilsson O. Rapid bone and blood flow formation in impacted morselized allografts: positron emission tomography (PET) studies on allografts in 5 femoral component revisions of total hip arthroplasty. *Acta Orthop Scand* 2003; **74**: 633-43.

123. Williams DF. A model for biocompatibility and its evaluation. *J Biomed Eng* 1989; **11**: 185-91.

124. Lind M et al. Transforming growth factor-beta stimulates bone ongrowth. Hydroxyapatite-coated implants studied in dogs. *Acta Orthop Scand* 1996; **67**: 611-6.

125. Soballe K et al. Migration of hydroxyapatite coated femoral prostheses. A Roentgen Stereophotogrammetric study. *J Bone Joint Surg Br* 1993; **75**: 681-7.

126. Ingham E, Fisher J. Biological reactions to wear debris in total joint replacement. *Proc Inst Mech Eng [H]* 2000; **214**: 21-37.

127. Fuchs S, Wieder J. [Survival rate of the cemented Charnley total hip endoprosthesis and modifying parameters]. *Biomed Tech (Berl)* 2000; **45**: 362-9.

128. Garellick G, Malchau H, Herberts P. Survival of hip replacements. A comparison of a randomized trial and a registry. *Clin Orthop* 2000; **375**: 157-67.

129. Sugano N, Nishii T, Nakata K, Masuhara K, Takaoka K. Polyethylene sockets and alumina ceramic heads in cemented total hip arthroplasty. A ten-year study. *J Bone Joint Surg Br* 1995; **77**: 548-56.

130. Cuckler JM, Bearcroft J, Asgian CM. Femoral head technologies to reduce polyethylene wear in total hip arthroplasty. *Clin Orthop* 1995; **317**: 57-63.

131. Piconi C, Maccauro G. Zirconia as a ceramic biomaterial. *Biomaterials* 1999; **20**: 1-25.

132. Cales B. Zirconia as a sliding material: histologic, laboratory, and clinical data. *Clin Orthop* 2000; **379**: 94-112.

133. Boutin P, Blanquaert D. [A study of the mechanical properties of alumina-on-alumina total hip prosthesis (author's transl)]. *Rev Chir Orthop Reparatrice Appar Mot* 1981; **67**: 279-87.

134. Boutin P. [Alumina and its use in surgery of the hip. (Experimental study)]. *Presse Med* 1971; **79**: 639-40.

135. Dorlot JM, Christel P, Meunier A. Wear analysis of retrieved alumina heads and sockets of hip prostheses. *J Biomed Mater Res* 1989; **23**: 299-310.

136. Bizot P, Nizard R, Lerouge S, Prudhommeaux F, Sedel L. Ceramic/ceramic total hip arthroplasty. *J Orthop Sci* 2000; **5**: 622-7.

137. Nevelos AB, Evans PA, Harrison P, Rainforth M. Examination of alumina ceramic components from total hip arthroplasties. *Proc Inst Mech Eng [H]* 1993; **207**: 155-62.

138. Kim YH, Kim JS, Cho SH. A comparison of polyethylene wear in hips with cobalt-chrome or zirconia heads. A prospective, randomised study. *J Bone Joint Surg Br* 2001; **83**: 742-50.

139. Schuller HM, Marti RK. Ten-year socket wear in 66 hip arthroplasties. Ceramic versus metal heads. *Acta Orthop Scand* 1990; **61**: 240-3.

140. Clarke IC, Gustafson A. Clinical and hip simulator comparisons of ceramic-on-polyethylene and metal-on-polyethylene wear. *Clin Orthop* 2000; **379**: 34-40.

141. Allain J, Le Mouel S, Goutallier D, Voisin MC. Poor eight-year survival of cemented zirconia-polyethylene total hip replacements. *J Bone Joint Surg Br* 1999; **81**: 835-42.

142. Boutin P et al. The use of dense alumina-alumina ceramic combination in total hip replacement. *J Biomed Mater Res* 1988; **22**: 1203-32.

143. Bizot P, Banallec L, Sedel L, Nizard R. Alumina-on-alumina total hip prostheses in patients 40 years of age or younger. *Clin Orthop* 2000; **379**: 68-76.

144. Smith-Petersen M. Evolution of mould arthroplasty of the hip joint. *J Bone Joint Br* 1948; **30-B**: 59-75.

145. McKee GK, Chen SC. The statistics of the McKee-Farrar method of total hip replacement. *Clin Orthop* 1973; **95**: 26-33.

146. McKellop HA, Sarmiento A, Schwinn CP, Ebramzadeh E. In vivo wear of titanium-alloy hip prostheses. *J Bone Joint Surg Am* 1990; **72**: 512-7.

147. Amstutz HC et al. Metal on metal total hip replacement workshop consensus document. *Clin Orthop* 1996; **329 Suppl**: S297-S303.

148. McKellop H et al. In vivo wear of three types of metal on metal hip prostheses during two decades of use. *Clin Orthop* 1996; **329 Suppl**: S128-S140.

149. Doorn PF et al. Metal wear particle characterization from metal on metal total hip replacements: transmission electron microscopy study of periprosthetic tissues and isolated particles. *J Biomed Mater Res* 1998; **42**: 103-11.

150. Firkins PJ et al. Quantitative analysis of wear and wear debris from metal-on-metal hip prostheses tested in a physiological hip joint simulator. *Biomed Mater Eng* 2001; **11**: 143-57.

151. Brodner W et al. Elevated serum cobalt with metal-on-metal articulating surfaces. *J Bone Joint Surg Br* 1997; **79**: 316-21.

152. Visuri T, Pukkala E, Paavolainen P, Pulkkinen P, Riska EB. Cancer risk after metal on metal and polyethylene on metal total hip arthroplasty. *Clin Orthop* 1996; **329 Suppl**: S280-S289.

153. Jacobsson SA, Djerf K, Wahlstrom O. Twenty-year results of McKee-Farrar versus Charnley prosthesis. *Clin Orthop* 1996; **329 Suppl**: S60-S68.

154. Toni A, Willmann G. *Bioceramics in Joint Arthroplasty.*: Thieme, 2001.

155. McKellop HA et al. The origin of submicron polyethylene wear debris in total hip arthroplasty. *Clin Orthop* 1995; **311**: 3-20.

156. Campbell PA, Wang M, Amstutz HC, Goodman SB. Positive cytokine production in failed metal-on-metal total hip replacement. *Acta Orthop Scand* 2002; **73**: 506-12.

157. Goodman SB et al. Cellular profile and cytokine production at prosthetic interfaces. Study of tissues retrieved from revised hip and knee replacements. *J Bone Joint Surg Br* 1998; **80**: 531-9.

158. Chiba J, Rubash HE, Kim KJ, Iwaki Y. The characterization of cytokines in the interface tissue obtained from failed cementless total hip arthroplasty with and without femoral osteolysis. *Clin Orthop* 1994; **300**: 304-12.

159. Lassus J et al. Increased interleukin-8 (IL-8) expression is related to aseptic loosening of total hip replacement. *Arch Orthop Trauma Surg* 2000; **120**: 328-32.

160. Xu JW et al. Interleukin-11 (IL-11) in aseptic loosening of total hip replacement (THR). *Scand J Rheumatol* 1998; **27**: 363-7.

161. Xu JW et al. Tumor necrosis factor-alpha (TNF-alpha) in loosening of total hip replacement (THR). *Clin Exp Rheumatol* 1996; **14**: 643-8.

162. Konttinen YT et al. Transforming growth factor-beta 1 and 2 in the synovial-like interface membrane between implant and bone in loosening of total hip arthroplasty. *J Rheumatol* 1997; **24**: 694-701.

163. Xu JW et al. Macrophage-colony stimulating factor (M-CSF) is increased in the synovial-like membrane of the periprosthetic tissues in the aseptic loosening of total hip replacement (THR). *Clin Rheumatol* 1997; **16**: 243-8.

164. Streich NA, Breusch SJ, Schneider U. Serum levels of interleukin 6 (IL-6), granulocyte-macrophage colony-stimulating factor (GM-CSF) and elastase in aseptic prosthetic loosening. *Int Orthop* 2003; **27**: 267-71.

165. Al Saffar N, Khwaja HA, Kadoya Y, Revell PA. Assessment of the role of GM-CSF in the cellular transformation and the development of erosive lesions around orthopaedic implants. *Am J Clin Pathol* 1996; **105**: 628-39.

166. Kim KJ, Rubash HE, Wilson SC, D'Antonio JA, McClain EJ. A histologic and biochemical comparison of the interface tissues in cementless and cemented hip prostheses. *Clin Orthop* 1993; **287**: 142-52.

APPENDIX A

Bearing materials

	Polyethylene
Introduction	Ultra high molecular weight polyethylene (UHMWPE) was introduced in orthopaedics as a bearing material in artificial joints for more than forty years ago [4]. UHMWPE articulating against a metallic femoral head has been the standard bearing material combination for total joint arthroplasty since its introduction in 1961 by Sir John Charnley. Polyethylene is a polymer formed from ethylene. For an ultra-high molecular weight polyethylene, the molecular chain can consist of as many as 200.000 ethylene repeat units. Metal-polyethylene is the classic Charnley bearing combination and today the most frequently used.
Advantages	Although good evidence of wear problems, the material has been used in total hip arthroplasties for more than 40 years. More than 90 % of the patients do get pain relieve and increased mobility after the operation.
Annual wear rate	The annual wear rate of metal-polyethylene is 0.2 mm/year [105].
Grain size	0.3-0.5 μm [126].
Disadvantage	The wear material has a capability to induce foreign body response and aseptic loosening. The hard on soft material combination is combined with a high wear rate on the soft bearings that may result in penetration of the polyethylene liner.
Previous Studies	Studies of polyethylene bearings revealed acceptable survival of 78.3% (Charnley) after 10 years [127], 93.2% (Charnley) and 95.9% (Spectron) after 11 years [128]. The relationship between long-term femoral head penetration and osteolysis was examined in a 10-year follow-up study [92]. In 48 patients with a primary total hip arthroplasty the 2D head penetration was measured. The true wear rate averaged 0.18 mm/year. In 9 hips with a true wear rate of less than 0.1 mm/year no osteolysis were identified. Osteolysis developed in 9 of 21 hips with a wear rate between 0.1 and 0.2 mm/year, in 8 of 10 hips with a rate between 0.2 and 0.3 mm/year, and in all eight hips with a rate of more than 0.3 mm/year [92].

	Polyethylene – Alumina/Zirconia
Introduction	Polyethylene against a ceramic head is the second most used bearing combination. The hard ceramic may be more resistant to scratches compared to metal femoral heads [129,130]. Zirconia ceramic was introduced in 1985 [131], due largely to its higher strength when compared to alumina. The main application of zirconia ceramics in hip implants is as femoral heads. Pure zirconia exhibits three phases a monoclinic, tetragonal, and cubic phases [105]. A phase change results in a volume change that affects the mechanical properties and the ceramic might crack [105]. For this reason, zirconia is with the addition of magnesia (Mg-PSZ) or yttria (Y-TZP) [105]. The chemical composition of Y-TZP is about 5.1% yttria (Y_2O_3) and 93-94% zirconia (ZrO_2) [132]. Alumina ceramic was developed in the early 1970-ies in France by Boutin [133,134]. In 2000 more that 3 million ceramic heads and since the middle 1980ties more than 200000 alumina cup inserts have been implanted [106]. The designs of the implants have changed as the purity of the ceramics has been developed continuously.
Advantages	The bearing combination was facilitated because of polyethylene wear was reduced significantly compared to metal/polyethylene *in vivo* and *in vitro*. The reduced wear rate may reduce the number of cases with wear debris induced aseptic loosening of hip implants.
Annual wear rate	The annual wear rate of alumina/polyethylene and zirconia/polyethylene is 0.1 mm/year [105]. The ceramic head against polyethylene liner has compared to metal reduced the linear wear rate with approximately 50%. The *in vivo* wear rates for first-generation ceramic components was 3-9 µm/year for linear wear [135,136] and 1-5 mm^3/year for volumetric wear [137]. In retrieved second-generation alumina - alumina combinations was 0.005 mm/year for linear wear [106]. Simulator tests of today's improved alumina ceramics are 0.001 mm/year for linear wear [106].
Grain size	The grain size for Y-TZP is <0.5µm and the grain size for Mg-PSZ is 30µm. The grain size of alumina was < 2µm [105].
Disadvantage	Zirconia heads has a higher fracture toughness (Y-TZP 8Mpa $m^{½}$) compared to alumina (4Mpa $m^{½}$) [105]. Because of this zirconia head sizes are offered in 22 mm, which alumina is not [105]. The fracture rate in the new generation of Alumina heads are reduced significantly compared to the first generation. In 2001, St. Gobain Desmarquest had to withdraw its international sales of orthopedic ceramic products, including Denmark. In one batch of zirconia femoral heads there were in vivo fracture rate of 33%. Because of sensitivity to parameters and humidity zirconia cannot be resterilised. As a mean the revision rate due to fractures was in vivo, in 1998 approximately 0.03 % [105].

Previous Studies

Survival rates in previous studies (Alumina/zirconia/metal against polyethylene): A prospective study in 70 patients with bilateral simultaneous total hip arthroplasties: one side with a cobalt- chrome (22 mm) femoral head and the other side with zirconia (28 mm) femoral head articulating with a Hylamer liner [138]. At a 6.4 years follow-up no components had been revised for aseptic loosening. The mean linear wear rate and annual wear rate were highest in the zirconia head, 1.25 mm (0.21 mm/year) and lowest in the cobalt-chrome head, 0.70 mm (0.12 mm/year). Osteolysis was identified on both sides of the acetabulum in six patients (9%). Of 12 hips with acetabular osteolysis, six had a cobalt-chrome femoral head and the remaining six a zirconia head [138]. The results of 28 mm and 22 mm heads are not completely comparable.

Schuller and Marti demonstrated results in line with these results. A 9-11 years follow-up was performed in 66 patients [139]. In 33 patients, the femoral head was ceramic and in 33 patients, the femoral head was metal, and all were articulating with a polyethylene liner. The average wear rate of the polyethylene was 0.26 in the ceramic group and 0.96 mm in the metal group. Radiological and clinical loosening was similar between the two groups [139].

Clarke and Gustafson reviewed laboratory and clinical studies comparing metal and ceramic heads articulating with polyethylene [140]. They concluded that data showing the superiority of ceramic-polyethylene were few. Further, the different polyethylene material and design combination used confounded the clinical results [140].

Zirconia: Allain et al reported a poor eight year survival rate of 63% using a cemented total hip arthroplasties with a zirconia head, a titanium alloy stem and a polyethylene cup [141]. At a mean of 5.8 years (1 to 9), aseptic loosening was seen in 11 hips (14%) [141].

By introduction of ceramic a mushroom shaped head was produced [106]. The range of motion of this head was below 90 degrees because of impingement and it resulted in subluxation. The impingement resulted in microfractures of the collar neck. The revision rate due to fractures was in vivo in 1998 approximately 0.01-0.02 % [105].

Alumina: Boutin reported a survival rate of 88% of a cementless alumina cup after 8 years with a 1.6% average annual probability of revision. The percentage of surviving was 100% after 8 years in patients younger than 50 years [142]. The main reason for revision was osteolysis. Boutin related this to a stress protection secondary to the high rigidity of the ceramic leading to a weakening of the spongious bone supporting the cement mantle [142].

Alumina-alumina has been recommended for younger patients because of the low wear rate and to avoid polyethylene wear.

In patients younger than 40 years with alumina-alumina bearings, Bizot reported an eight year survival rate between 88.8% and 95.1% with different cups. After 10 years, the survival rate was between 90.4% and 88.8% with different cups [143]. The follow-up period was from 2-22 years and the wear rate was beyond measure. Bone graft was the only prognostic factor, with a survival rate of 62.6% after 10 years for the hips with a bone graft and of 90.1% for hips without a graft [143].

Long-term prospective and randomised studies with identical components and a high number of patients will be necessary to measure differences in survival.

	CoCr-CoCr
Introduction	Metal (CoCr alloys) have been used for hip replacement since 1938, when it was introduced in the Smith-Petersen hemi arthroplasty [144]. One of the first to introduce the first generation of metal-metal bearings in total hip replacements was McKee and Watson-Farrar [7,145]. Today second generation metal-metal bearings have been developed in order to reduce the wear rate. A variety of metallic biomaterials have been used for femoral heads in joint arthroplasty as titanium and stainless steel [146].
Advantages	The advantages of these bearings were a very low wear rates, and no risk of fracture of the metal components. The accuracy of the surface in the second generation metal-on-metal is very excessive and the bearings are self-polishing [9].
Annual wear rate	The clinically volumetric wear rate is 1-5 mm^3/y [147], which is very low compared to polyethylene articulating to metal. McKellop found an average linear wear of 6 μm/year and a volumetric wear of 6 mm^3 of metallic wear debris per year [148]. Semlitsch et al. reported an annual wear rate of 2-20 μm/year [107].
Grain size	The wear particles in metal-on-metal articulations range between 6 nm and 5 μm [149,150].
Disadvantage	There has been some concern whether the metal-on-metal bearings could induce hypersensitivity to metal because of the long-term exposure to metal ions. S-cobalt levels were measured and compared in 55 patients (27 CoCrMo and 28 ceramic-on-polyethylene) before and after implantation a total hip arthroplasty [151]. After one year, the S-Cobalt was significantly higher in the metal-on-metal group (median 1.1 μg/l) compared to the ceramic-on-polyethylene control group (median below detection limit of 0.3 μ/l) [151]. The incidence of cancer after metal on metal total hip arthroplasty has also been a concern. Patients with metal-on-metal and polyethylene-on-metal bearings in total hip arthroplasty were compared with the general population in Finland [152]. The mean follow up time for the patients who had metal on metal total hip arthroplasty was 15.7 (9092 person years) and for the patients who had polyethylene on metal total hip arthroplasty it was 12.5 years (19846 person years). The leukaemia rate and the other forms of cancers did not differ statistically significant from those in the general population [152].
Previous Studies	Survival rates in previous studies: Jacobsson et al reviewed 107 consecutive McKee-Farrar and 70 Charnley total hip arthroplasties performed in 169 patients. At the 20 years follow-up (range, 19-21 years), 29 patients with 20 McKee-Farrar and 11 Charnley prostheses were available. Radiographic signs of loosening were present in 52% of the surviving prostheses. The long-term results of the two implant in this study were comparable and Jacobsson suggested that the second generation all metal implants was worth considering in patients with long life expectancy [153].

Friction and Wear

Another advantage to the alumina – alumina combination is a very low friction coefficient. This allow compromises between advantages and disadvantages between a large or a small femoral head.

One advantage to a small femoral head diameter is a lower friction torque. The friction torque, M_t transmitted from head to the cup interface is [154]:

$$M_t = \mu WD/2$$

Where:
μ = head-liner friction coefficient;
W = Joint load;
D = Head diameter

Second advantage to a small femoral head diameter is a reduced volumetric wear. The approximate correlation between volumetric and linear wear can be calculated in the equation;

$$V = \pi D^2/4 \text{ x linear wear}$$

Intending to have as low friction and wear as possible Charnley introduced a 22 mm femoral head [4].

The disadvantages of a small femoral head were decreased range of motion and risk of dislocation.

As the head-liner friction coefficient in a ceramic-ceramic joint is about 1.3 times smaller compared to polyethylene-metal the head size was of less importance to the friction torque, M_t and annual volumetric wear, V. Meaning that, an increased ceramic head diameter will increase range of moment without increasing volumetric wear.

Particle generation

Wear particles from the bearing materials can occur in four different wear modes [155].

Mode 1. Wear particles created at the intended bearing materials by *abrasion*.

Mode 2. Wear particles created at the femoral head and the acetabular metal backing because of a penetrated liner.

Mode 3. As mode 1 but in the presence of a third body component (e.g. cement particles)

Mode 4. Wear particles produced between two non-bearing materials (e.g. backside of the polyethylene and the acetabular metal backing).

Particles may also develop away from the bearing materials such as the stem or cement particles in loose implants.

APPENDIX B

List of cell mediators known to influence bone remodelling

Stimulates bone resorption	Stimulates bone formation	Inhibits bone resorption	Inhibits bone formation
IL-1β	IL-1	IL-1	IL-1
IL-6			IL-6
IL-8			
IL-11			IL-11
TNF-α			
TGFβ			
RANKL			
		OPG	
M-CSF			
GM-CSF			
PDGF	PDGF		
PGE-2	PGE-2		
VEGF			
	EGF		

Literature review of cytokines

The cytokines found to be elevated in the pseudosynovial membrane and interface tissue from aseptic loose hip arthroplasties compared to non-inflamed control tissue. Method of evaluation has been by media of cultures or by immunohistochemistry of the tissue.

Cell mediator	Pseudosynovial membrane	Interface membrane
IL-1β	156	157
IL-6	156	157,158
IL-8	159	159
IL-11	160	160
TNFα	161	161
TGF-β	162	162
RANKL/RANK/OPG	82	82
M-CSF	163	163
GM-CSF	164	165
PDGF	158	
PGE-2	166	27
IGF-I		
VEGF		86

APPENDIX C

Paper I-III