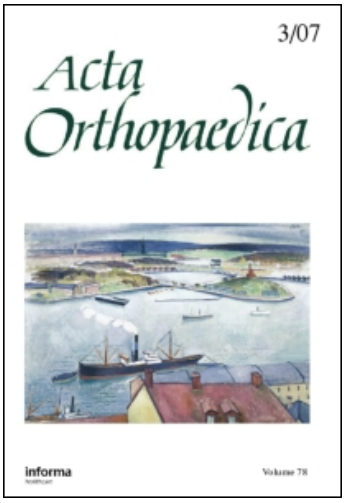

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Hydroxyapatite ceramic coating for bone implant fixation

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Introduction

Clinical background

The use of total hip and knee arthroplasty is steadily increasing (3). It has been estimated that world-wide 2.5 million patients are living with an artificial hip joint (120) and that 800,000 total hip arthroplasties are performed each year.

The development of bone cement as a filler between bone and hip prosthesis (74) was a revolutionary step in orthopedics in the 1960s since the short-term results were excellent with consistent relief of pain and disability. However, long-term results revealed an increased rate of mechanical loosening in younger active patients and patients with rheumatoid arthritis, whereas the revision rate in older patients is significantly lower even after 15 years (3, 14, 59, 75, 135, 298, 311).

Improvements in cementation techniques have reduced the incidence of mechanical loosening (27, 142, 206, 232, 299) and latest new types of bone cement with a lower curing temperature might further improve the long term survival of the cemented prostheses (144, 145, 219, 227).

Indeed, great demands are made on total joint replacements. The load transmitted on hip and knee prostheses may be up to 6 times body weight and because of the inherent biological and biomechanical properties of bone cement, young active patients will usually outlive the fixation of the prosthesis. Thus, there is widespread concern about the considerable risk of failure, especially because of the subsequent need for even more difficult operative treatment with less beneficial results (71, 139, 153, 254, 287, 308).

These facts have resulted in increased interest in other principles for implant fixation, first of all by means of biological fixation to the bone without the use of bone cement (118).

Several different types and designs of non-cemented prostheses are available but so far there is no evidence suggesting that non-cemented joint replacements perform better than cemented ones. A significant percentage of patients with non-cemented hip replacement have persistent thigh pain and limbing (106) and retrieval studies of non-cemented metal porous coated hip and knee prostheses have revealed that many of the components had become fixed to the skeleton by fibrous tissue ingrowth instead of bony ingrowth (44, 80, 81, 86, 107). For these reasons great efforts have concentrated upon enhancement of bony ingrowth into the prosthetic surface. Special interest has focused on the ceramic material hydroxyapatite (HA) which recently has been successfully coated onto a metal surface using a plasma spray technique (93, 122, 316).

Purpose of experimental studies

The purpose of the present series of experimental studies was systematically to evaluate potential improvements of bone implant fixation using hydroxyapatite (HA) ceramic coating.

Gap-healing

In the clinical situation, initial direct apposition of implant to bone is often limited to relatively small areas (269) and most of the porous coated area of femoral components lacks initial osseous contact (231). Anatomical variations in the bone, (230) deficient implant design, and poor surgical technique are factors responsible for the presence of gaps between the implant surface and surrounding bone. The first step in a series of studies on implant fixation therefore focused on (I)

- enhancement of bone ingrowth across a gap between bone and implant by HA-coating compared with implants inserted in press-fit.

Osteopenic bone bed

Like most other studies on bone ingrowth the first study (I) was performed on healthy young animals where bone ingrowth occurs in high percentages. Because many patients with joint disease have a deficient bone stock as seen in osteoporosis, prolonged steroid treatment and rheumatoid arthritis, the next challenge in this series of studies called for a new experimental model of osteopenia. A reproducible experimental model of unilateral arthritis (58) was adapted after a study on (II):

- juxtaarticular bone loss in experimental arthritis of the knee using CT scanning for quantitative measurements of bone density.

This model of osteopenia was applied to study (III, IV)

- the influence of osteopenia of the host bone bed on the fixation of titanium alloy (Ti) and HA-coated implants inserted in press-fit.
- the effect of HA-coating on the gap healing capacity of osteopenic bone.

Bone grafting

The use of bank bone allograft in endoprosthetic surgery has recently gained increasing importance, particularly in cementless reconstruction of failed arthroplasties where direct fit to host bone cannot be obtained because of loss of bone stock around the loose implant (137, 147, 164, 216, 264, 332). Furthermore, disease states of the bone resulting in increased resorption activity, as seen in rheumatoid arthritis, (177) may affect the strength of biological fixation, (279) and will often require bone grafting for stabilization of cementless prostheses. No previous studies have investigated the combined effect of bone grafting and HA-coating.

We therefore created a new model to study bone graft incorporation into porous coated implants (V) and analyzed

- the incorporation of allogeneic bone graft into Ti and HA-coated implants compared with implants without bone graft.
- the influence of arthritic host bone changes on the incorporation of allogeneic bone graft into Ti and HA-coated implants.
- the effect of HA coating on implant fixation in osteopenic and control host bone when surrounded by a 2-mm gap.

Mechanical stability

An important factor underlying inferior bone implant fixation might be the presence of relative motion between implant and bone bed. Studies of cementless hip- and knee prosthetic components implanted into cadaver bone have shown micromovements of 100–600 µm (49, 56, 273, 286, 341, 343). These movements might be responsible for development of a fibrous membrane, as evident in retrieved non-cemented hip and knee prostheses from humans (44, 80, 81, 86, 107).

Since the magnitude of micromotion and its effect on bone tissue is difficult to assess in clinical practice, we found it important to create a dynamic system to study the significance of controlled micromovements between bone and implant.

In this model we analyzed (VI, VII)

- the host tissue response around porous coated Ti- and HA-coated implants subjected to controlled relative movements between implant and bone compared with stable implants.
- the influence of type of tissue ingrowth on the mechanical fixation of the implant.

The implants were subjected to 150-µm and 500-µm movements during each gait cycle (VI, VII). These studies showed that unstable mechanical conditions around porous coated implants prevented bony ingrowth and resulted in development of a fibrous tissue membrane. These membranes consisted predominantly of fibrocartilage around HA-coated implants whereas fibrous connective tissue was found around Ti implants. However, several unanswered questions arose concerning the long term course of these fibrous membranes. We therefore performed a final experiment (VIII)

- to study further the course of a motion-induced fibrous membrane around Ti and HA-coated implants when subjected to continuous load.
- to investigate the effect of immobilization of fibrous anchored Ti and HA-coated implants.

The following survey will focus on assisting the understanding of the effect of hydroxyapatite coating in bone tissue when subjected to pathological and mechanical conditions mimicking the clinical situation.

Definitions

Biomaterials

In recent years, several terms have evolved within the science of biomaterials. Because of this, a Consensus Conference was held at the European Society of Biomaterials in 1986 (348, 349) where some of these terms were defined. Definitions of terms relevant for this thesis are presented here.

Bioactive material: a material which has been designed to induce specific biological activity.

Biocompatibility: the ability of a material to perform with an appropriate host response in a specific application.

Biomaterial: a non viable material, used in a medical device, intended to interact with biological systems.

Host response: the reaction of a living system to the presence of a material.

Implant: a medical device made from one or more biomaterials that is intentionally placed within the body, either totally or partially buried beneath an epithelial surface.

*Allograft:** a graft taken from another individual of the same species as the recipient.

*Autograft:** a graft taken from a source in the individual who receives it.

*Biodegradation:** the gradual breakdown of a material mediated by specific biological activity.

*Bioresorption:** the process of removal by cellular activity and/or dissolution of a material in a biological environment.

Bone ingrowth: many terms have been used to describe the biological response around non-cemented implants: bone ingrowth, bone ongrowth, osseointegration, biological ingrowth etc. In the present studies, the term bone ingrowth has been selected to describe bone tissue in direct contact with the implant surface at the light-microscopic level.

**Provisional agreement reached at the meeting, but subsequent reservations have been made (348, 349).*

Technical definitions

Load: The external force (F) applied to a material.

Shear: The motion of two parallel surfaces relative to each other.

Strain: Deformation of a body divided by its original length (dL/L).

Stress: The force per unit area that develops within a body in response to externally applied forces (F/A), (MPa).

Ultimate strength: The maximum stress which a material can withstand before failure (MPa).

Apparent shear stiffness: The relation between applied load and deformation obtained during push-out test, represented by the slope of the load-deformation curve (MPa/m) (Figure 1).

Energy to failure: Energy absorption at the interface before failure measured from the area beneath the load-displacement curve until failure. The energy absorption is normalized by the length of the implant specimen tested (J/m) (Figure 1).

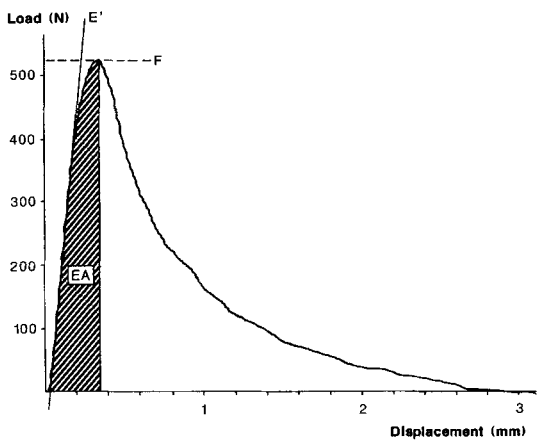


Figure 1. Load deformation curve from the push-out test. F is the maximum force applied to the implant during the push-out procedure, E apparent shear stiffness and EA energy absorption until failure.

Biomaterials

Classification of biomaterials

A biomaterial is defined as a non viable material, used in a medical device, intended to interact with biological systems (348, 349).

The biotolerant implants (bone cement, stainless steel, Co-Cr) are surrounded by a connective tissue layer between implant and surrounding bone because the tissue responds by encapsulating these inert materials in fibrous tissue.

The bioinert implants (alumina, zirconia, carbon materials, titanium) are characterized by direct contact between implant and surrounding bone. These materials are characterized by a stable oxide layer at the surface.

The bioactive implants (certain glass ceramics, calcium-phosphate ceramics) are characterized by a direct chemical bond between implant and surrounding bone.

Biomaterials can also be classified according to their chemical composition in

- ceramics
- metals
- polymers
- composites

The following description will focus on characteristics for ceramics and metals.

Ceramics

According to Heimke, ceramics in material science comprise all nonmetallic and inorganic materials (149).

Ceramics used for implants are of three types: 1) oxide ceramics, 2) calcium-phosphate containing glass ceramics and glasses, and 3) calcium phosphate ceramics (149).

Oxide ceramics. Representatives of the oxide ceramics are alumina (Al_2O_3) and zirconia (ZrO_2). These ceramics constitute bioinert ceramics which have excellent tribological properties. Today, a ceramic ball on the stem combined with a conventional polyethylene socket is available in most hip systems. This combination has a very low friction and favorable wear behavior (271). Ceramic/ceramic articulations have the lowest wear rate.

Glass ceramics. The glasses used for implants are based on silica (SiO_2) and the principle in glass-ceramics is that soluble calcium phosphate ions are incorporated into the "bioglass" ceramic structure. After implantation, a layer of HA is formed on the surface which provides a chemical bond between tissues and the implant surface (152).

Calcium phosphate ceramics. Much attention has focused on ceramics which resemble the mineral phase in bone tissue i.e. hydroxyapatite, octacalcium phosphate and tricalcium phosphate (149). These ceramics are termed bioactive ceramics. Probably the most interesting bioceramic development in recent years is the use of bioactive calcium phosphate coatings onto pros-

Table 1. Classification of biomaterials with respect to the biological response as suggested by Osborn (241)

Biodynamics	Implant material	Reaction of host bone	Implant interface
1. Biotolerant	Bone cement, stainless steel, Co-Cr alloy	Distance osteogenesis	Connective tissue layer between implant and bone
2. Bioinert	Alumina, Zirconia Carbon materials, Titanium	Contact osteogenesis	Direct contact between implant and bone
3. Bioactive	Ca-PO4 ceramics (hydroxyapatite) Glass ceramics	Bonding osteogenesis	Chemical bond between implant and bone

Table 2. Time taken (days) for apatite formation on different ceramics

Compound	Days
Hydroxyapatite	30
Tricalcium-phosphate	14
Glass ceramic	7
P_2O_5 containing glass	1/4

Glass-ceramic = Na_2O 5, CaO 33, SiO_2 46, $Ca(PO_3)_2$ 16 wt%
P_2O_5 containing glass = P_2O_5, CaO-SiO_2

thetic components. A general characteristic of calcium-phosphate ceramics is their ability to become directly bonded to bone (166).

It has recently been demonstrated that ceramics form an apatite layer on their surfaces in a simulated body fluid. This apatite formation occurs at different time periods depending on type of ceramic, as shown in Table. 2 (187, 233, T. Yamamuro, personal communication).

Preparation of calcium phosphate ceramics

Tricalcium phosphate (TCP) is formed by precipitation of calcium phosphate at physiological pH and temperature (243). TCP is autocatalytically transformed into a crystalline form of HA when it comes into contact with water (41).

TCP has a beta whitlockite lattice, and HA is crystallographically characterized as an apatite after sintering (185).

Pure HA powder is available commercially with the chemical formula:

$$Ca_{10}(PO_4)_6(OH)_2$$

and a stoichiometric Ca/P molar ratio of 10/6 = 1.67.

For preparation of a ceramic block of HA, the HA powder is compressed into the desired form and sintered at temperatures up to 1250 °C (120). Temperature is very critical as the crystallographic structure is retained only up to 1300 °C, higher temperatures resulting in phase transitions of HA so giving increasing amounts of tricalcium phosphate (TCP) which has different biological and physical properties (243), i.e.

$$Ca_{10}(PO_4)_6(OH)_2 \rightarrow 3\,Ca_3(PO_4)_2 + CaO + H_2O$$

TCP has been shown to have a lower osteogenic potential (186) and be less stable than HA (185). Concerning biocompatibility of TCP one study has shown that TCP resulted in inflammatory reactions and inhibited osseous repair in rabbits tibia (245). In contrast, many other studies have demonstrated enhanced osseous repair and no adverse tissue reactions of TCP coated implants (70, 185).

Hydroxyapatite

The term "apatite" refers to a broad family of structurally related compounds (HA, fluorapatite, chlorapatite etc) (252). The term apatite is derived from a Greek word meaning "to deceive" which indicates that early researchers were deceived and confused when investigating HA (243).

HA ceramic is available for clinical use in 3 forms: as a bulk material, as granules or as a thin coating on metal substrates (243).

Bulk materials

Bulk materials are available in porous and dense forms. The porous material allows for bone ingrowth but is less resistant to applied mechanical load compared to the dense material (240). Porous blocks of HA have been used with success for augmentation procedures in edentulous patients (158). The limitations of bulk materials are the poor mechanical properties due to these materials being very brittle. They have high resistance for purely compressive forces, but relatively low bending and shear strength (243). Therefore, implants consisting of HA cannot be applied in situations where forces other than pure compression exist, e.g. in a joint prosthesis. Bulk material can be used as granular bone fillers (e.g. ear, nose, and throat implants, replacement of hearing ossicles, reduction of alveolar ridge height) for sites where loads are limited to pure compression (149, 238).

Hydroxyapatite coating

In the late 1980s, techniques were developed allowing HA to be sprayed onto a metallic substrate. This combination makes it possible to use HA for joint prostheses because coating materials can be used for implants with high mechanical requirements. Several processes have been used (for review see Berndt; 36). The most commonly used process of coating HA is plasma spraying.

Plasma spraying of hydroxyapatite

Plasma spraying of HA was first described by de Groot in the late 1980s (93). The principle for plasma spraying is that HA particles are injected into a plasma tail flame with a high temperature (15,000 °C). The flame source is a plasma gun consisting of two electrodes

creating an electric arc. A gas (usually argon or hydrogen) flow through the space between the electrodes where it is ionized to form a plasma (155). The HA particles are accelerated to a high velocity (approximately the speed of sound [300 ms^{-1}]) when injected in the plasma flame and are driven against the surface of the substrate. The HA particles partially melt in the plasma flame and solidify on impact against the metal substrate, a layer of particles being built up. To improve the bonding, the metal substrate is roughened beforehand by grit blasting, bead blasting or abrasion.

Many variables are determinative for the quality of the coating. These include the heat content and velocity of the plasma flame, particle size of HA powder, pressure of the carrier gas and the distance between the gun and the surface to be coated (155). The nature and properties of the powder affect all stages of the plasma spray process.

The optimal temperature of the plasma flame is especially important since too high a temperature may result in overheating of the HA particles causing them to vaporize. On the other hand, if the temperature is too low the particles will not be sufficiently melted before impacting the substrate resulting in unbonded particles in the lamellar structure. Overheating without vaporizing may result in conversion of HA to TCP and CaO.

Several factors may weaken the coating. Cracks, entrapped air, oxidized overheated particles and unmelted particles may reduce the mechanical strength of the coating. The density of HA-coating is particular important, as a small reduction in density will reduce the mechanical strength significantly. Many more variables may weaken the bond between HA and metal (for review see Jones; 172).

To improve the adhesive strength, plasma spraying may be performed under vacuum to obtain a denser coating and a high adhesive strength to the substrate (36)

Quality of hydroxyapatite coating

Great variability in the quality of HA-coating on different prostheses from different companies may be expected and it is highly recommended that surgeons using HA coated prosthetic devices request a quality report for each batch delivered before inserting the prosthesis.

Recently, Anderson et al. (16) suggested that all manufacturers of HA coated prosthetic devices adopt a common assurance program including relevant analysis of HA-coating in order to be able to trace a prosthetic device and distinguish between successful and unsuccessful cases.

Factors of importance for the behavior of HA-coating include

- Chemical composition (purity)
- Ca/P ratio
- Crystallinity
- Microstructure (density)
- Adhesive strength relative to the implant
- Thickness of coating
- Trace component analysis

The coating thickness of HA is often discussed. The thickness is theoretically a compromise between the mechanical properties and dissolution of the coating. The mechanical properties (toughness) increase with decreasing thickness of the coating as the probability of finding defects is reduced. This may improve the fatigue strength of the coating. The amount of HA lost has been calculated to be 15 μm within the first year (338) after which stabilization occurs when bone has covered the surface. At present there is general acceptance that a 50–75 μm coating is preferable due to lower risk of HA fracture and preservation of porous structure of the implant surface (93, 122), but thicker coatings have also been recommended and are clinically widely used (239). Coatings as thin as 1 μm have been made (36). A relatively thin coating is necessary to avoid obstruction of the pores in the substrate-coating.

Other general agreements regarding HA-coating seem to be that purity of HA should be as high as possible (95–97%), crystallinity 70–90% and Ca/P ratio 1.67. Bond strength between HA and substrate varies from 5 MPa to 65 MPa depending on the condition of the metal substrate (36, 120, 316). Fatigue life of greater than 10^7 tensile cycles at 8.3 MPa has been reported (121).

X-ray diffraction analysis is used to assess the purity of HA. An X-ray beam passes through the crystals producing a diffraction pattern which is related to the crystal lattice in the irradiated material. The angle between the incoming X-ray beam and the diffracted beams can be measured by placing a film near the irradiated sample (252). Each peak represents a diffracted beam. The easiest way to identify impurities is to overlay the graph of the component of the pure ingredient suspected to be an impurity and look for the dominant reflection. The sharpness of the peaks is related to the crystallinity of the product. Narrow sharp peaks indicate crystalline material whereas broad peaks with low intensity against an uneven and noisy background indicate amorphous materials. A value for crystallinity can be obtained by measuring the integrated intensity of the four main peaks between 30 and 35 degrees (146).

The main metal substrate for HA-coating presently used is Ti alloy (Ti-6Al-4V) which is less susceptible to corrosion than most other metals and has a lower elastic modulus. Regarding the elastic modulus, the strain

between the HA-coating and the metal substrate is minimized when the modulus of both components is as close as possible (36). Recently, prostheses with HA-coating on Co-Cr substrate have been introduced on the market and HA has also been coated on polysulfone femoral components (210).

Biodegradation

An important concern of HA-coating is its degradability in the biological environment.

It is well known that tricalcium-phosphate (TCP) is more resorbable that HA (184). Biodegradation is a function of a) composition (purity) b) porosity, and c) crystallinity of the coating. Also the physiological environment is a important factor for resorption of HA. Dense coatings with high crystallinity seem to be less resorbable compared to coatings with micropores and less crystallinity (184). Presence of TCP in the HA-coating might also contribute to increased resorption. Resorption of HA probably occurs by both solution mediated processes and cell-mediated processes (184).

The stability of HA in the biological environment is still controversial. Some studies have reported resorption of HA (165, 339) whereas others have concluded that biodegradation of HA does not occur (184). Cook et al. (89) measured the thickness of HA-coating in an unloaded transcortical dog model at time zero to 32 weeks postimplantation and found no reduction in thickness during the implantation period. Klein (184) showed that dense and porous HA was stable in bone tissue after 9 months. In contrast, Van Blitterswijk (338, 339) found resorption of porous HA in the first months after implantation in the rat middle ear to average 15 µm. Resorption of HA has also been observed in rabbit tibial implantation after 3 months (165). Bagambisa et al. (22) recently observed osteoclastic resorption of the HA surface after 6 months in Alsatian femora, as evidenced by Howship's-like lacunae into the HA surface.

Currently, there seems to be general agreement that some of the HA-coating is resorbed in the initial phase after insertion during the process of bone formation around and at the HA surface (92, 120, 165). Geesink (120) suggested that resorption of HA will continue at a rate of approximately 15 µm a year if not covered by bone tissue. This is in agreement with the finding that degradation of HA may occur when implanted in soft tissue (subcutaneously in rabbits) (184).

Results from retrieval studies of hip implants from human patients (29, 39, 117, 140, 239, 301) suggest focal cell mediated resorption of HA (29), and a study from our laboratory has shown that bone continued into the HA-coating without the appearance of any clear boundary suggesting that the exogenous coating of HA has been dissolved (301). Hardy et al. found no resorption or variation in thickness of HA-coating (140). Geesink demonstrated that minor parts of HA were resorbed after 2 years in human retrieval specimens and also that HA was preserved if covered by bone whereas resorption was most often found at sites where fibrous tissue covered the implant surface (RGT Geesink, personal communication).

In the present study (VIII) 77% of the HA-coating was resorbed after 16 weeks when implants were subjected to continuous micromotion/load. The amount of resorption was greater than expected and may be explained by presence of micromovements since immobilization of implants reduced the amount of HA resorption to 56% (VIII). An important finding was that 25% of the resorbed HA was replaced by bone.

Regarding HA resorption in animals it should be emphasized that the bone remodeling rate of dogs is 2–3 times faster than in humans suggesting a higher activity and resorption of HA in dogs compared with human patients (182).

Recently, fluorapatite coated implants have been studied in trabecular bone in goats and compared with HA-coating (96). Both types of coating were covered by bone without fibrous tissue being present. Degradation of HA was demonstrated after 12 weeks (though not quantified) whereas no degradation of fluorapatite was apparent.

Whether the HA-coating will be completely resorbed from loaded implants in the long run is unknown and the clinical effect of HA resorption has still to be elucidated. In the author's opinion, resorption of HA would be of minor significance. Bone would grow into the porous metal surface and anchor the implant after a stable situation has been achieved by the HA-coating, this resulting in optimal conditions for "osseointegration". This phenomenon was demonstrated in paper VIII, where 25% of the resorbed HA-coating was replaced by bone which had grown up to the surface of the metal porous coating. It is therefore important that the metal substrate used is biocompatible in order to allow "osseointegration" (for example c.p. Ti) (170).

In conclusion, the question about resorption of HA has not been elucidated, and long-term studies focusing on this problem are lacking. Moreover, the clinical effect of HA resorption remains to be elucidated.

Interfaces

Two interfaces are of interest regarding HA-coated implants: 1) the HA-metal interface, and 2) the HA-bone interface.

HA-metal interface

Under optimal conditions, the coating is firmly anchored to the substrate (120, 155). Bond strength between HA and substrate varies from 5 MPa to 65 MPa depending on the condition (i.e. roughness etc) of the metal substrate (36). Failure between HA-coating and substrate has been reported 32 weeks after implantation (316). The failures appeared at 12 MPa load which was less than the in vitro measured strength of HA substrate bond (17 MPa) and might suggest a weakening of HA substrate bond strength during implantation. However, these failures only occurred on the crest of the grooves on the implant which indicates that implants should be designed to protect the HA-coating that might otherwise be pulled off the metal under applied loads. This was the rationale for depositing HA on implants with a porous coating in the present studies. However, a thin HA-coating is necessary to avoid obstruction of the pores in the substrate metal coating.

Failure with breakdown at the interface between HA and Ti alloy substrate has been reported after 4, 8, and 12 weeks in a loaded dog model (272). HA was coated onto grit blasted smooth Ti alloy rods; the thickness of HA-coating was 80–100 μm, the purity 98% (according to manufacturer) and the porosity 20%. Similar findings have been demonstrated using Co-Cr implants as substrate in a non-loaded model (228). Peeling-off of HA from the metal substrate has also been described when HA is coated on a flat surface. However, when HA was coated on a surface of porous beads, such problems were eliminated (236). These findings are in strong contrast to retrieval studies on HA-coated prostheses from human patients. At present, 6 papers including 15 HA-coated femoral prostheses retrieved up to 2 years after surgery have been published and no delamination has been reported (29, 39, 117, 140, 239, 301). Since the majority of the large number of experimental studies on HA-coating has not encountered problems in obtaining intact HA-substrate contact after observation times up to 18 months, the failures reported might be ascribed to a poor quality of HA-coating.

HA-bone interface

Histological and mechanical evaluations have repeatedly confirmed the positive influence of HA-coating on bone ingrowth and anchorage. At the light microscopic level calciumphosphate has been shown to be non-toxic and non-inflammatory when inserted into bone tissue (29, 89, 93, 95, 120, 122, 123, 167, 184, 313, 316). Also at the ultrastructural level, no inflammatory cells have been detected around a HA-coated implant in bone (94). Examination of the ultrastructure at the bone-titanium implant interface from rabbit and clinically retrieved implants have revealed a 100 nm wide dense osmiophilic line i.e. a lamina limitans (108, 268). Electron microscopy examination of the bone-hydroxyapatite interface after 3 months in rat femurs has revealed a direct chemical bonding between bone and HA without any unmineralized tissue layer at the interface (327). Therefore on the atomic scale, there seems to be evidence that bone grows directly onto the surface of HA.

Absence of any inflammatory reaction from surrounding tissues may be explained by the fact that HA is not considered as a foreign material (which normally will be sequested by fibrous encapsulation) but rather as a physiological bone component because of its resemblance to bone.

Strength of fixation of HA-coated implants

Most experimental studies evaluating the fixation of HA-coated implants have been performed on non-weight bearing implants inserted in press-fit. Insertion into slightly overdrilled holes (0.1 mm) has also been used, and finally gap healing capacity has been studied in larger gaps (1–2 mm). Weight bearing models have also been applied to study the effect of HA-coating.

Representative published shear strength values from papers comparing HA and non HA coated implants are given in Table 3.

It is difficult to compare strength of fixation between studies due to differences in implant types, anatomical localization, observation period, weight bearing and testing conditions. However, some clear trends do emerge. Studies on non-weight bearing porous non-HA-coated implants have shown that the maximum attachment strength between porous coated implants and bone is developed after 8–12 weeks (47, 62, 88). In contrast, HA-coated implants are reported to obtain maximum strength after 5 weeks in cortical bone (89). Thus, the maximum interface shear strength is obtained in half the time as compared with porous coated implants without HA-coating (17, 90). Furthermore, during unstable mechanical conditions, fixation of fibrous anchored HA implants is obtained in 1/4 of the time required for the equal fixation of implants without HA-coating (VI, VII).

HA-coating has been demonstrated to enhance implant fixation from 2 weeks up to 70 weeks after implantation (237, 250).

Table 3. Shear strength values (MPa) from HA-coated and non HA-coated control implants with different observation periods

Obs. (weeks)	Shear strength −HA	+HA	Control	Implantation	Load	Effect[d]	References
2	0.5[c]	1.3	Ti alloy	gap	–	^	Oonishi et al. (237)
3	7.7[c]	7.5	c.p. Ti	press-fit	–	–	Cook et al. (88)
	1.5[a]	4.0	c.p. Ti	press-fit	–	+	Cook et al. (89)
	4.4[b]	6.0	c.p. Ti	press-fit	–	+	Thomas et al. (316)
4	2.6[c]	5.7	Ti alloy	gap	–	+	Søballe et al. (303)
	7.0[c]	6.7	Ti alloy	press-fit	–	–	Søballe et al. (303)
	10.1[c]	7.5	Ti alloy	press-fit	–	–	Søballe et al. (305)
	1.6[c]	4.6	Ti alloy	gap	–	+	Søballe et al. (306)
	0.6[c]	2.2	Ti alloy	gap	+	+	Søballe et al. (302)
	0.7[c]	7.2	Ti alloy	gap	+	+	Søballe et al. (297)
	1.5[c]	4.4	Ti alloy	gap	–	^	Oonishi et al. (237)
5	4.8[b]	9.6	c.p. Ti	press-fit	–	+	Thomas et al. (316)
	0.9[a]	7.0	c.p. Ti	press-fit	–	+	Cook et al. (89)
6	12.6[c]	14.2	c.p. Ti	press-fit	–	–	Cook et al. (88)
	1.5[a]	7.0	c.p. Ti	press-fit	–	+	Cook et al. (89)
	7.5[c]	14.1	Ti alloy	gap	–	^	Oonishi et al. (237)
	0.5[c]	4.8	Ti alloy	gap	–	+	Søballe et al. (304)
10	10.5[b]	14.1	c.p. Ti	press-fit	–	+	Thomas et al. (316)
	1.0[a]	7.3	c.p. Ti	press-fit	–	+	Cook et al. (89)
12	18.1[c]	17.9	c.p. Ti	press-fit	–	–	Cook et al. (88)
	25[c]	25	Ti alloy	gap	–	^	Oonishi et al. (237)
	7.4[a]	13.3	Ti alloy	press-fit	–	+	Dhert et al. (97)
16	1.8[c]	4.6	Ti alloy	gap	+	+	Søballe et al. (307)
25	9.6[a]	17.3	Ti alloy	press-fit	–	+	Dhert et al. (97)
32	1.2[a]	6.0	c.p. Ti	press-fit	–	+	Cook et al. (89)
70	0.01[a]	1.9	Ti alloy	press-fit	+	+	Poser et al. (250)

[a] bead or grit blasted
[b] macrotextured
[c] porous coated
[d] Effect: + significantly stronger interface shear strength of HA implants
– no significant difference
^ statistics not reported

In the present studies, different shear strength values were obtained (I, III-VIII). This may be explained by differences in coating quality and thickness of coating, but also implantation site in relation to the stress direction in the distal femur might be responsible.

Strength of fixation of metal implants

The general course of screw fixation in cortical bone is a decrease during the first week followed by a static period during the second week and then an increase in fixation from 3–12 weeks (234). According to Sumner and Galante (290), the initial fixation of porous coated implants is less than that obtained with bone cement, but after 2 weeks the fixation strengths are equal (195, 290).

Regarding implantation in cancellous or cortical bone it has been shown that implant fixation is about six-fold stronger in cortical bone than in trabecular bone (290). However, peak values in cortical bone are delayed to 8 weeks whereas peak values in cancellous bone are reached at 2 weeks, probably due to the faster bone remodeling in cancellous bone.

Metals

Current implant materials

The most commonly used metal implants in orthopaedic application are stainless steel, cobalt-chrome, c.p. Ti and Ti alloy.

Stainless steel

Stainless steel contain about 20% chromium and 17%

nickel. The type most used is 316L (ASTM) which has adequate mechanical properties for medical implants. Stainless steel used for non-cemented arthroplasties with porous coating has not been successful (91) because of the relatively poor corrosive characteristics.

Cobalt-chrome

Cobalt-chrome alloys have been used in medical application since 1930s and constitute a large part of orthopaedic implants used today. These alloys contain 30% chromium and 70% cobalt. Co-Cr alloys appear to be the most corrosion and fatigue resistant of all implant alloys. Only Ti is superior with respect to corrosive resistance (78).

Titanium and titanium alloy

The third metal type used as implant material is commercially pure (c.p.) Ti and Ti alloy. C.p. Ti is characterized by a high corrosive resistance, and Ti has also been shown to be particularly biocompatible (10, 50). Another attractive property is the elastic modulus of Ti which is closer to that of cortical bone as compared to other implant materials which might reduce non-anatomical bone remodeling around the prosthesis caused by stress shielding. However, the elasticity of Ti is 5 times greater than that of bone. The inferior mechanical properties of pure Ti led to the development of Ti alloy (Ti-6Al-4V) which has superior mechanical properties and similar corrosive resistance whereas the elastic modulus is unchanged (176). These properties might increase the fatigue life compared to c.p. Ti.

Ti is rapidly oxidized when exposed to oxygen (174) and a stable oxide surface will always exist on a Ti implant in clinical use. This means that tissue around the implant surface is exposed to a ceramic Ti oxide surface and not directly to the Ti metal.

Surface treatment of metal implants

The surface can be left smooth, be textured (e.g. grooved) or treated with different kinds of coatings. The coating may consist of metal, polymer, glass or ceramics.

The first implant with a porous surface was developed in 1968 (156), several different techniques and coatings being developed during this period. The porous Ti fiber metal was reported in 1971 (118). Porous polymers and ceramics were also studied at this time but porous metals were the materials of choice for biological fixation (282).

Biomechanical properties of porous materials

The mechanical compatibility of porous metals with bone (118) is considered to be advantageous due to an improvement in stress distribution to the surrounding bone. The bonding between the porous material and the solid metal substrate has been studied extensively and changes in porosity (247) and sintering temperatures and pressures (103) have improved the strength between the porous coating and metal substrate.

Porous coating

The term "porous" refers to a series of interconnecting channels (pores) located on the implant surface. These pores are produced by coating a layer of small particles (beads, fiber, powder) onto the metal surface. The porous coating was primarily developed for non-cemented use, as bone was expected to grow into the pores thereby anchoring the implant to the skeleton. The theoretical background for the porous coating was to increase the surface area thus providing a larger contact area to the bone which would anchor the implant by ingrowth and result in an optimal stress distribution to the bone.

Clinically, the metallic coatings have been the most used types, but polysulfone and polyethylene have also been used (280).

Porous coating involves some kind of increased heat treatment of the metal cores, but this can be disadvantageous as the heat may affect the microstructure of the metal substrate (176). These problems have resulted in many different techniques of coating the implant. The most common methods for applying porous coating is the sintering process, diffusion bonding and plasma spraying.

Sintering technique is used to form a porous coating composed of spherical beads. The beads are bonded to each other by a sintering process which requires heating of the entire component at high temperatures. However, this high temperature may result in reduced mechanical properties of the metal substrat. The currently available prostheses with this coating are Co-Cr alloy beads on Co-Cr substrate or c.p. Ti beads on Ti alloy substrate. Loosening of the beads from total knee components has been reported (257).

Diffusion bonding is used for Ti fiber metal onto a Ti alloy substrate and is performed under pressure and a lower temperature than sintering. Ti fiber pads are made by cutting Ti wire into short strands which are then molded together and pressed into shape.

Plasma spraying is different from the two other techniques as a heated metal powder form is sprayed onto the substrate. In this process only the powder to be sprayed onto the substrate is heated which reduces heating of the substrate. Temperature, pressure and

atmosphere determine the texture of the coating. Metal used for this process in currently available prostheses is Ti alloy onto Ti alloy substrate.

Pore size. The pore size obtained by sintering technique ranges from 150–350 μm and the porosity is 30%. The wire mesh has an average pore size of 350 μm and the plasma spray technique results in a mean pore size of 300 μm.

Corrosion

The least corrosion resistant of the metals used in orthopaedic clinics is stainless steel. Ti and Co-Cr are more resistant to corrosion because of metal oxides adhere to their surfaces (258).

Metal ions

Liberation of metal ions from implant surfaces has been reported in retrieval studies (2) which has led to concerns about the increased surface area of porous coated implants. Concerning Ti alloy (Ti,Al,V) in vitro studies have shown that aluminum delayed the formation of hydroxyapatite but also Ti and V resulted in a decrease of hydroxyapatite formation (40, 42). (For further details see review by Johansson (170) on adverse effect by metal ion release).

Ion implantation

Regarding metal ion release from the porous surface, medical tribology (i.e. lubrication, friction and surface wear in joint replacement) are also important factors which contribute to release of particles to the surrounding tissues.

Ion implantation provides a method for improving the durability of metal surfaces. The process of ion implantation involves bombardment of the target with ions which arrive at high velocity, penetrate the surface and rest in the lattice of the target metal. Ion implantation of gliding surfaces manufactured from Ti-6Al-4V reduces the wear rate (258) and also the corrosion wear is reduced by ion implantation (351). For further details see review by Röstlund (258).

Biological background

Bone repair

Under optimal conditions, bone tissue has the capability to repair an injury without scar tissue formation. As the process of bone ingrowth into porous coated implants has been compared with fracture healing (283, 290), a brief summary of bone repair and fracture healing will here be given.

The process of bone repair can be divided into three sequential phases.

Inflammatory phase. Following accumulation and coagulation of hematoma within the fracture space an acute inflammatory response occurs with vasodilatation and exudation of plasma and leukocytes followed by macrophages.

Reparative phase. In this phase the fracture hematoma is invaded by fibrovascular tissue (revascularization) which replaces the hematoma. Devitalized necrotic bone is resorbed by osteoclastic recruitment. Osteocytes do not take part in the repair process but mesenchymal cells from periosteum and endosteum differentiates into bone forming or cartilage forming cells depending on the microenvironment at the fracture site. This fibrous and cartilaginous callus envelops the bone ends and increases the stability of the fracture fragments. The callus is subsequently replaced and woven bone is formed by intramembranous or endochondral ossification (267). Many factors are involved in callus formation and bone healing, and an overview of this subject has been presented by Simmons (118). Under optimal stable conditions the fracture can also heal via direct bone formation without a cartilaginous phase (73).

The process of bone ingrowth into porous-coated implants has been shown to occur via direct bone formation when inserted in press-fit (51). However, when surrounded by a gap, a cartilagineous phase will probably occur prior to bone (218).

Remodeling phase. Following woven bone formation, an internal reorganization (remodeling) starts by which new lamellar bone is formed with a functional orientation.

In animals, the inflammatory phase takes place during the first few days, the reparative phase with woven bone occurs after 2 weeks and the remodeling phase begins about 4 weeks after surgery (118, 290). A new complete repair with structural normalization may occur as soon as after 6–8 months (188).

Healing of bone defects (gap healing)

Healing of cortical bone defects is very different from fracture healing (218). Small holes may be integrated in micro-repair phenomenon which may be integrated in remodeling. Healing of larger bone defects occurs via endochondral ossification with a cartilaginous phase which is later replaced by bone (218). Johner (171) studied healing of cortical bore holes in rabbits and reported that holes of 200 µm in diameter were filled exclusively by lamellar bone, larger holes (400 µm) being initially filled by woven bone (171). Healing of holes greater than 1 mm in diameter is considerably delayed because woven bone cannot bridge the gap in one step (267). This is in agreement with fracture healing where the critical gap size (resulting in nonosteonal bone union) seems to be within the limit of 1 mm (267).

Dependency of mechanical stability

The outcome of fracture healing depends on the initial mechanical stability of the fracture (136). Rigidly fixed fractures without gaps heal via direct bone formation, whereas unstable mechanical conditions at the fracture site may result in healing via a cartilaginous phase followed by endochondral ossification (20, 72, 73, 192). The final outcome of unstable mechanical conditions may be non-union with the presence of a fibrous tissue layer between the fracture ends which may be analogous to the fibrous membrane developed around the unstable implants in the present study. The generally accepted hypothesis for these events is that differentiation into osteoblasts demands a high oxygen tension, whereas differentiation into chondrocytes occurs where the oxygen tension is low (28). The microenvironment at the fracture site therefore seems to determine the type of tissue formed in the reparative phase.

Certain theories exist concerning the development of different types of tissues in the fracture gap. Pauwels (244) hypothesized that there is a causal relation between mechanical stressing and differentiation of the supporting tissues, as tension is the specific stimulus for development of collagen fibers and compression (hydrostatic pressure) for the development of cartilaginous tissue. Another theory termed the "interfragmentary strain theory" (246) hypothesizes that the type of

tissue formation in the fracture gap is a function of the magnitude of strain (i.e. the relative deformation) in tissues in the fracture gap. Thus, even minor motion in a small fracture gap results in high strain values and consequently the development of a fibrous tissue layer between the fragments. The fibrous tissue in the fracture gap may reduce the strain to a level where cartilage formation is possible which will further reduce the strain to a level where bone formation is possible.

In conclusion, reaction to a fracture may occur in three ways: 1) primary healing, 2) secondary healing via chondral ossification and 3) non-union (pseudarthrosis). Regarding the process occurring around porous coated implants, there seems to be a certain parallelism with an outcome depending on, among others, the mechanical stability and loading conditions on the implant.

Methodological considerations

Several points must be considered when evaluating results from the present studies. Design errors, biological variation and test conditions may all influence the results obtained. A discussion of the methods used for obtaining and evaluating the results is separated into:

1. Choice of experimental animal
2. Design of studies
3. Implants (geometry, size, surface area)
4. The micromovement device
5. Implantation
6. General postoperative measurements
7. Preparation of specimens
8. Histological analysis
9. Biomechanical testing
10. Evaluation of fibrous membrane
11. CT-scanning
12. Statistics

Choice of experimental animal

An animal model is advantageous because it is possible to separate the complex clinical situation into different well defined elements which can be controlled so allowing the study of isolated problems.

Figure 2. Dog with micromotion device in both knees.

Studies of orthopedic implants demand a certain size of experimental animal, the mature Labrador dog (Figure 2) having the appropriate size. Furthermore, the dog is often used for studies on implant fixation because its bone structure is close to that of humans (104, 116). Moreover, dogs have previously been used in our research group for studies on experimentally induced arthritis (58) which was also applied in the initial studies to investigate bone ingrowth from an osteopenic bone bed (II, III, IV, V). Labrador dogs of known age were delivered in litters (up to 7 dogs in each litter) which was advantageous as this minimized interindividual variation. The animals were bred for scientific purposes and the care and use of these laboratory animals complied with the Danish law on animal experimentation.

Design of studies

Different designs were used for the different studies according to the particular question given highest priority.

In all studies, each dog was used as its own control by comparing implants inserted in the right knee with implants in the left knee. In some studies implants in lateral condyles were compared with implants in medial condyles for less important questions (I, V, VI). Comparison between implants inserted in medial and lateral condyles may be criticized as bone turnover and density may differ in these two bone compartments. However, we found bone density in the lateral and medial condyles to be equal in study V (but not in study I) before implantation. Furthermore, in the recent studies the compared implants were randomly allocated to the medial or lateral condyles (VI) to compensate for incidental differences in bone turnover at the two implantation sites. Alternation between the right and left leg was used in the studies on micromovements (VII, VIII) to eliminate incidental differences in load bearing on the left and right knee.

In the CT-study (II) the design was matched based on differences between the experimental arthritic knees and control knees using each dog as its own control. A similar design was used in most other studies (I,

III–VII, VIII) but, in addition, these studies (except I and VI) were based on comparison between two groups of dogs. However, the groups were matches according to sex, age, and weight (III–V, VII, VIII) and bone density measured was comparable in the compared groups (III, IV, V).

Two basically different implant models were used. An unloaded model was used in studies I–V whereas in studies VI–VIII a loaded model was used. The unloaded model was employed to study the fixation of HA- and Ti-coated implants during standardized conditions without possible variations in load pattern of the implant. The model was, however, not completely unloaded, as studies on transcortical implants have shown remodeling of trabeculae around the implants suggesting that at least some load is applied to the implants (280).

Observation time. The observation period varied between 4 weeks (I–IV, VI–VII), 6 weeks (V), and 16 weeks (VIII). The choice of observation time was adapted from some of the first published studies on HA-coating which demonstrated a time dependent effect of HA-coating, as fixation seems to equalize with values observed without HA-coating by 12 weeks observation time (102).

Sample size. The sample size used for the experiments was likewise based on other studies on HA-coating where the fixation by HA-coated implants was shown to be 170–700% stronger compared with Ti coated implants (89, 316). A 200% effect of HA would result in a power of the experiment of more than 80% using a sample size of 6 with a standard deviation of 50% of the mean value. The risk of an error of the second kind (ß) was selected to 20% and the risk of an error of the first kind (2α) to 5% (15).

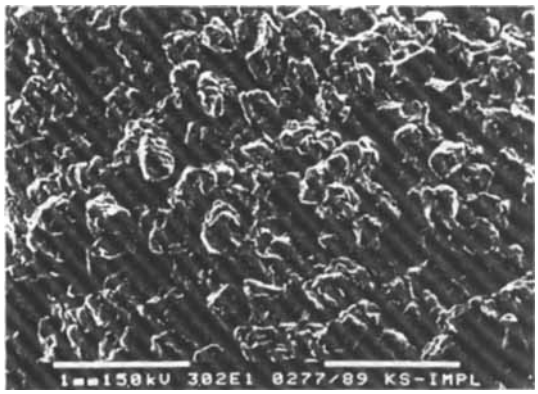
Implants

Geometry. A cylindrical form of the implants was chosen because preparation of the host bone site by drilling a hole is easily standardized compared with, for example, preparation for a plate or a squared implant form. The cylindrical form is also optimal for the push-out test as the implant is pushed into a similar but slightly larger cylindrical hole.

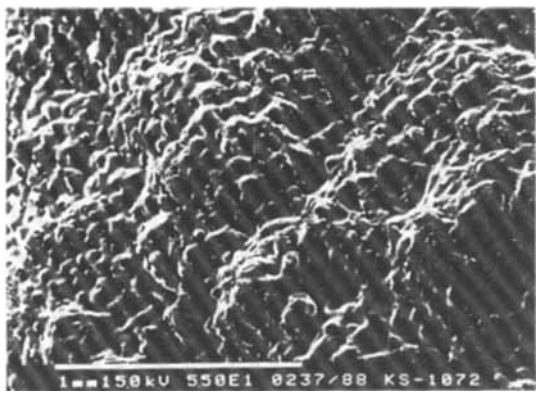
Size. Since the implants were to be placed in the femoral condyles in the first studies, the size of the implants was confined to 6 mm in diameter as larger implants would exceed the volume of the epiphyseal bone.

Surface area. It is obvious from the first studies (I, III, IV, V) that the HA-coated implants have a relatively smoother surface (Figure 3B) compared with those of Ti-coated implants (Figure 3A) whereas only minor

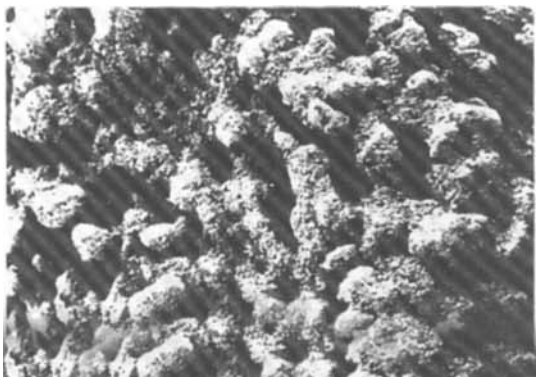
Figure 3. Scanning electron microscopy of the surface of the implants.



A. The surface of a Ti-coated implant used in all studies (I– VIII). Note the porous structure. Original magnification x30.



B. The surface of an HA-coated implant used for studies I–V. Note the pore obstruction after a 200-µm thick HA-coating. Original magnification x50.



C. The surface of an HA-coated implant used for studies VI–VIII. Note the preservation of pores after a 50-µm thick HA-coating. Original magnification x30.

Table 4. Surface roughness of Ti-coated and HA-coated implants (μm)

Surface roughness	R_a		P_t	
Study	I–V	VI–VIII	I–V	VI–VIII
HA implants	21	41	265	445
Ti implants	38	47	352	496

differences were present in the last studies (VI–VIII) (Figure 3C). Measurements of the total surface area of implants used for studies I, III, IV and V were performed using a videoplan and showed approximately 50% larger surface area of Ti-coated implants than HA-coated implants with 200-μm thick coating. Push-out values normalized for these surface area calculations showed that the relative difference between HA- and Ti-coated implants was 2-fold stronger as compared with calculations based on the diameter of the implant alone. The published push-out data therefore underestimate the effect of HA-coating. Differences in surface area probably also account for the discrepancy between push-out values and bone ingrowth, the last parameter demonstrating a stronger effect of HA-coating (I).

Underestimation of the effect of HA-coating in the initial studies is indirectly confirmed by data presented in the latter studies (VI, VII, VIII) where a thinner HA-coating and a greater surface area further increased the relative differences in anchorage between Ti and HA-coating.

The surface roughness of Ti and HA-coated implants was determined using a roughness-meter with a stylus tip radius of 3 μm. R_a (international parameter of roughness) is the arithmetic mean of the departures of the roughness profile from the mean line. The profile depth (P_t) is the maximum peak to valley height of the profile in the assessment length. These data seem to confirm the surface area measurements indicating a larger and more rough surface on Ti implants as compared to HA-implants in studies I, III–V. Only minor differences in roughness were present in studies VI-VIII (Table 4).

Titanium alloy coating. The Ti coating was applied using plasma spraying technique and implants used for each separate study were coated during the same procedure to minimize variations in coating specifications.

The pore size of Ti-coating was determined by a linear intercept technique (ASTM E-112, section 10) modified for two phase materials (section 13) at a magnification of 50x. The mean pore size approximated 300 μm (200 μm at substrate and 1000 μm at surface of the coating). Studies on HA-coating of course should be performed with the best alternative as a control. We used Ti alloyed implants as controls in the present studies (I–VIII), as have other investigators (120, 122, 123, 237), but commercially pure (c.p.) Ti has also been used (83, 88, 89, 313, 316) as controls where the fixation is up to 5–7 times inferior as compared with HA-coating (89).

Hydroxyapatite coating. The HA-coating for studies I–V was provided by one vendor and the HA-coating for studies VI–VIII from another vendor. The HA-coated implants consisted of a porous Ti-coating on which a layer of synthetic HA was deposited by the plasma spraying technique. In studies I, III–V the diameter of HA-coated implants was 0.4 mm larger than Ti implants. In studies VI–VIII the substrate implant was appropriately undersized to provide identical implant diameters after coating. The strength of attachment between the HA and the substrate for studies VI–VIII was determined by ASTM standard C-633 for cohesive strength of coatings to metal and revealed minimum tensile strength of 34 MPa and a minimum shear strength of 20 MPa. Results from X-ray diffraction analysis of the ceramic coating compared to ASTM powder diffraction standard 9-432 for HA are shown in Table 5. The crystallinity, Ca/P ratio and thickness of coating are also given for the two groups of studies. Sterilization by gamma irradiation did not change the purity of HA.

In studies I, III–V, the coating contained a small portion of ß-tricalcium phosphate (TCP). It is difficult to evaluate the effect of the presence of TCP on the tissue response around the implant, but comparisons between results from studies I–V and studies VI–VIII show a stronger effect of HA in the last studies with pure HA-

Table 5. Characteristics of HA coatings used in the different studies

Study	Tricalcium phosphate	Crystallinity of HA	Ca/P-ratio	Thickness of coating (μm)
I–V	trace (10 %)	mixture of amorphous and crystalline HA	1.65	150–200
VI–VIII	no	75 %	1.64–1.70	50–75

coating. Thus, presence of TCP might reduce some of the positive effect of HA on implant fixation. It should, however, be emphasized that other variables such as thickness of coating, surface area and loading conditions might contribute to the differences.

Trace component analysis revealed fewer than 500 ppm (parts per million) of extraneous elements.

The micromotion device

The dynamic device was modified, reconstructed and tested in several pilot studies before the final design was achieved.

The rationale for selecting 500 μm movements in the first study (VI) was that recent studies had reported relative bone-implant movements (rigid body motion) of 200–600 microns when testing cementless tibial trays (49, 273, 286, 343) and hip femoral components (341). More recently it was demonstrated that differences in elasticity between bone and the rigidly fixed metallic porous coated prosthesis alone might result in a tangential displacement of 150 μm at the periphery of tibial trays immediately after implantation (224, 355). These results encouraged us to perform one more study on 150 μm movements (VII).

The maximal movement in axial direction was predetermined and limited to the desired amount by the design of the device. However, as the degree of implant movement was not controlled throughout the observation period, stable control implants were used for comparison (VI, VII).

The tolerances in machining resulted in the desired displacements ± 15 μm. To ensure equal displacement and stiffness of the springs they were calibrated and adjusted prior to implantation by axially loading the implant on a universal testing machine and the displacement versus load recorded. Displacements were measured to be 490 (SEM 20) μm in study VI and 161 (SEM 36) μm in study VII before implantation. After implantation the displacement decreased equally with approximately 5% in all groups. No differences in displacement were encountered between compared groups. The calibration curves prior to surgery showed little resistance but following the implantation period there was an initial resistance of about 3 newtons, then unconstrained displacement to the maximum value. The elastic modulus was equal between the compared groups and the minor increment in stiffness which developed during the implantation period was ascribed to the presence of fibrous tissue surrounding the springs.

The elasticity in the springs was chosen to be relatively soft (14 N/mm) in order to avoid damage to the tibial articular cartilage but still stiff enough to push the implant back to the initial position.

The device was designed to permit axial movements, but small rotatory and rocking movements of the implants might have occurred. Therefore, pilot studies were performed using implants with blocked axial motion but allowing rocking and rotatory movements. These two movements were found to be negligible both in HA- and Ti-coated implants since bone ingrowth and fixation were equal to those of stable control implants.

Wear debris from the polyethylene plug might affect formation and characterization of the fibrous membrane developed around the unstable implants. However, no detectable wear of polyethylene was demonstrated in the polarization microscope. The polyethylene plugs were manufactured from ultrahighmolecular polyethylene (UHMWPE) being similar to those used in human patients (medical grade). The plugs were 25 μm less than the inner diameter of the centralizer and domed at one end to contact the tibial part of the knee. All implants were sterilized by gamma irradiation.

To avoid galvanic corrosion of the metal which might suppress the surrounding bone, all components in the dynamic device were manufactured from the same Ti alloy as the implant. Release of metal ions from the base of the piston might occur due to movements. However, the absence of metal ions around unstable HA implants, as demonstrated in study VII, suggests that no detectable metal was released from the dynamic device due to movements.

Only mild synovial inflammation secondary to implantation was found, as evidenced by synovial histology. The fact that only slight fibrillation of the tibial cartilage could be demonstrated was expected as the polyethylene plug was easily displaced in proximal direction when the knee was loaded.

Models for implantation

The site for implantation was selected in order to mimic the clinical situation including presence of a cancellous bone bed around the implant. We therefore chose the distal femoral epiphysis as the implantation site because it contains cancellous bone and also because it is affected by arthritic joint changes (58).

It is important to control the reproducibility of the implantation site since variation in the orientation of bone trabeculae and bone density might influence both biomechanical and histomorphometric parameters. We attempted to minimize inter- and intra-individual dif-

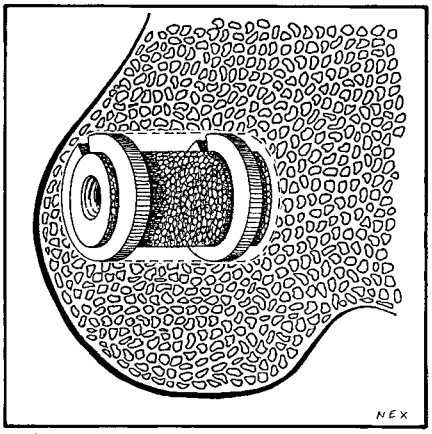


Figure 4. The gap model showing the implant which is centralized in the drill hole by two Ti spacers fixed at each end of the implant so permitting a 1 mm gap around the implant.

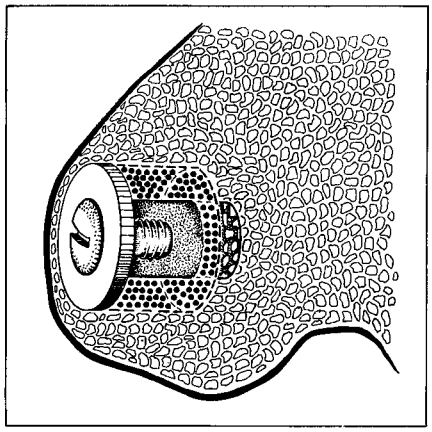


Figure 5. The bone graft model illustrating the implant centralized in the overreamed canal surrounded by a 2 mm gap allowing bone graft to be packed around the implant. The deep part of the implant is fixed in the bone by press-fit and a Ti washer keeps the graft in place and centralizes the implant superficially. Dotted area illustrates bone graft. Non-grafted implants served as controls.

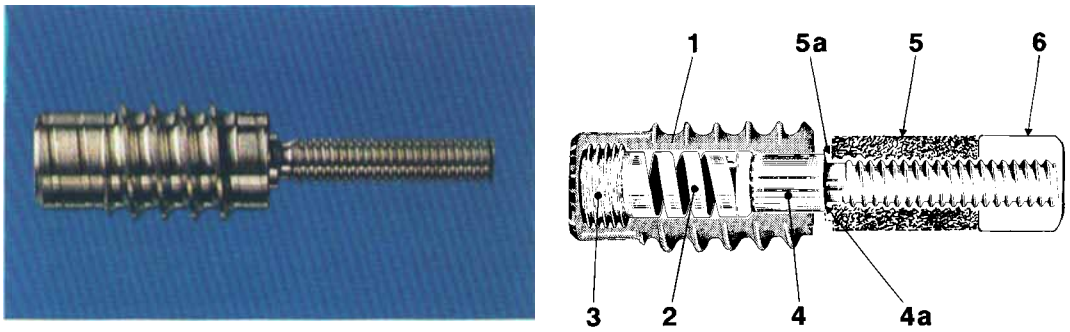


Figure 6. The micromotion device. The schematic drawing shows the device with test implant and polyethylene plug. The hollow Ti cylinder (1) has self tapping threads to ensure firm fixation in the bone. A spring (2) is placed inside the cylinder and held in place by an adjustable screw (3) at one end. In the other end a piston (4) can move freely in the axial direction. When mounted, the platform (4a) on the piston projects exactly 500 μm over the end of the Ti cylinder (1). When the test implant (5) is screwed onto the threads of the piston and axial load applied on the polyethylene plug (6), the test implant will move until it is stopped by reaching the Ti cylinder, the movement being limited to 500 μm. In order to prevent rotation of the piston, one end of the spring is fixed to the piston (4) and the other to the screw (3) which is locked into the Ti cylinder by a small polyethylene plug inserted into the threads of the screw. A hole through the piston and the polyethylene plug connects the compartment in the Ti cylinder with the knee joint. The coating is removed at the distal end of the implant (5a) in order to prevent bony ingrowth in this area.

ferences in implantations by adopting a standardized surgical procedure with landmarks combined with fluoroscopy.

Two basically different models were used, namely an unloaded and a loaded model. In the unloaded gap model the holes were drilled 2 mm larger than the diameter of the implant so permitting a 1 mm gap surrounding the implants which were centralized by two Ti spacers fixed at each end of the implant (Figure 4). The thickness of HA coating was taken into account in the selection of drill size. In the bone graft model, 2 mm overreaming was chosen to study incorporation of bone graft around implants. Larger gaps exist in the clinical situation, but the size of the femoral condyle in the dog model limited the gap to 2 mm which seemed adequate to inhibit bone ingrowth and gap healing around Ti-coated implants. The graft was added until the canal was filled and a Ti washer was mounted to keep the graft in place and to centralize the implant superficially (Figure 5).

For the loaded model a micromotion device was constructed, consisting of an implantable dynamic device (Figure 6) which was inserted into the knee joint as illustrated in Figure 7. The system was adjusted preop-

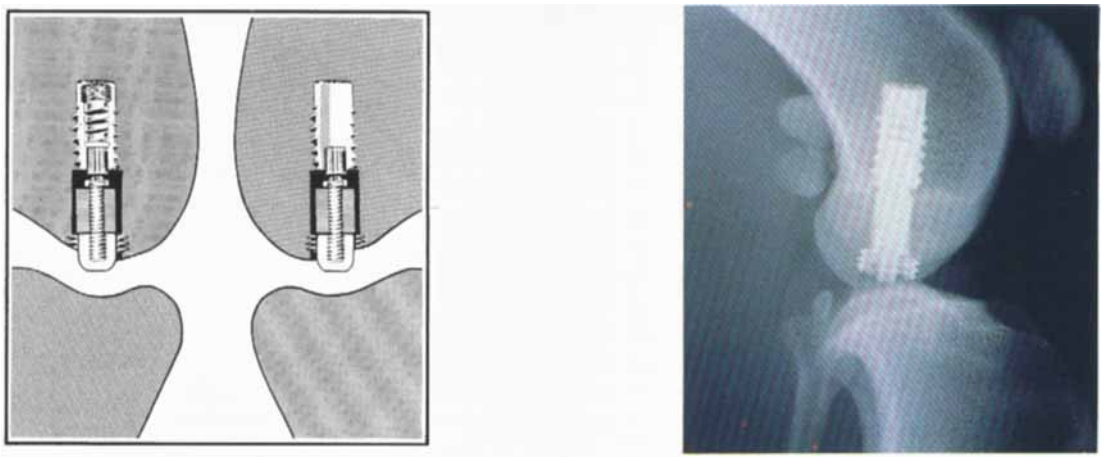


Figure 7. Schematic illustration and postoperative radiograph of the dynamic system inserted into the weight-bearing part of the medial femoral condyle. Details of the dynamic device are given in Figure 6. The polyethylene plug projects above the femoral articular cartilage. A Ti ring is mounted subchondrally and serves as a bearing and centralizer for the polyethylene plug. When the knee is loaded during gait, load transfer from the tibial part of the knee will displace the polyethylene plug and the test implant in axial direction and tighten the spring. When the leg is subsequently unloaded, the tightened spring will move the implant back to the original position. Thus, a controlled movement will occur during each gait cycle. A stable implant in the contralateral knee serves as control.

eratively to a stiffness of approximately 14 N/mm with a preload of 0.5 N, the total displacement force being 10 N. The maximal movements in axial direction could be predetermined and limited to the desired amount due to the design of the device. Movements of 500 µm and 150 µm were used. Stable implants served as controls.

The site of implantation of the micromotion device was selected in the central portion of the femoral condyles which contacts the meniscus and tibia plateau during the stance phase and the walking phase according to electrogoniometric studies of normal gait in dogs (1). From postmortem radiographic measurements in the present series, it was demonstrated that contact between the polyethylene and the tibial part of the knee was maintained within the range of 30–120 degrees of knee-flexion with the implantation technique used. Due to the surgical impact on the dogs only the medial condyles were used in the last two studies (VII, VIII). Following implantation, extension of the knee confirmed contact between the meniscus and the polyethylene plug and axial motion of the system could be visualized by axial load application on the tibia. The amount of projection of polyethylene was adjustable to allow exact positioning of the system in the joint contact area. Thus, when assembled and implanted controlled implant movements would occur during each gait cycle.

General postoperative registration and measurements

The dogs were regularly inspected with special attention to wound healing and weight-bearing. All animals were allowed immediate postoperative weight-bearing. In studies VI, VII, and VIII gait performance was registered regularly. The dogs stayed in individual cages measuring 1.5 x 2.5 meters, and were allowed out-door training three hours a day (1.5 x 3.5 meters).

Immediately postmortem the knees were opened under sterile conditions, the implants exposed and cultures taken from the implantation site and synovial fluid. Some positive cultures were registered and ascribed to contamination as no clinical signs of infection were evident.

Preparation of specimens

The cutting procedure was standardized to minimize variation in cutting level of the specimens for later comparison. All specimens were prepared and cut by the main author to minimize possible variation during these procedures. No problems were encountered in maintaining intact metal, ceramics, and tissue elements during cutting.

The grinding technique (99) used seems to be the best preparation method for quantitative evaluation of bone ingrowth using conventional light microscopy. The

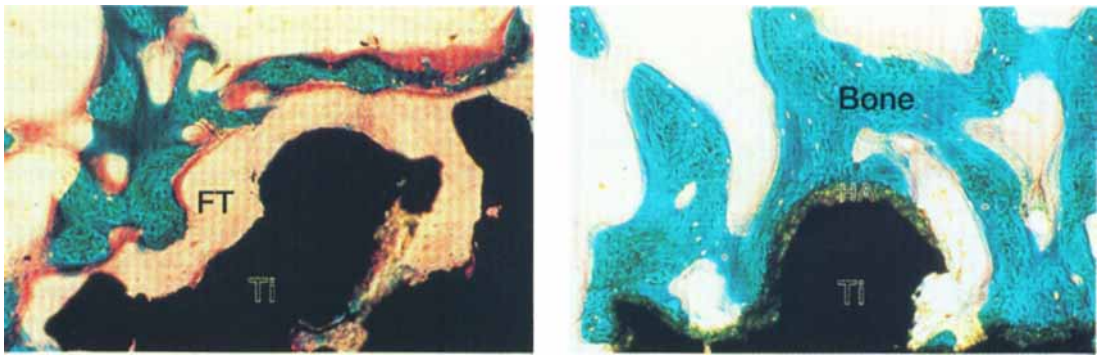


Figure 8. Photomicrograph showing the staining technique. Bone is stained green and fibrous tissue (FT) is stained red (left). Note that it is easy to differentiate between bone and HA (right). Basic fuchsin and light green; original magnification x100. Ti = titanium alloy, HA = hydroxyapatite.

only problem with the grinding procedure was that some implants which had been subjected to micromovements separated from the surrounding fibrous tissue membrane and repeated grinding procedures had to be performed to make successful sections.

Several other methods for preparation of sections for host-implant interface evaluation are available. Mechanical removal of the implant after embedding in metylmethacrylate has drawbacks, as a tissue layer at the interface might be removed together with the implant (201, 317). Another method is to remove the bulk metal by electropolishing after embedding the tissue-implant en block (38, 318). This technique has the advantage that specimens can be prepared for electron microscopic analysis, but has recently been shown to demineralize the surrounding bone (108).

Histological analysis

Histomorphometry. One important requirement for histological staining was a differentiation of bone from soft tissue. Therefore, we used a special staining technique described by Gotfredsen et al. (130) where the soft tissue was stained during dehydration in graduated ethyl-alcohol solutions from 70% to 99% containing 0.4% basic fuchsin. Bone was later counterstained with light green. This procedure provides sufficient contrast between bone and soft tissue (Figure 8).

The method is useful for conventional light microscopy but artifacts have been described in the form of white zones (65). These artifacts are very thin zones adjacent to the implant where no tissue is present. The zones are usually less than 1–10 μm which is less than the resolution level for light microscopy (approximately 10 μm under optimal conditions on 2 μm thin sections (65). Presence of white zones is considered to be due to differences in hardness between implant and surrounding tissue or shrinkage under the fixation process (65).

Another drawback of the technique used is the inability to perform a detailed analysis of cells in tissue around the implant because of the relatively thick sections. However, the main purpose of the study was not to analyze cells around the implants but to evaluate relative differences in bone and fibrous tissue apposition on the implant surfaces. Evaluation of the latter occurred with an acceptable accuracy on ground sections.

Another potential problem is difficulty in differentiating bone from HA-coating, since the latter also contains calcium and phosphorous and therefore also receives some of the green stain. However, we found no difficulties in differentiating between bone and HA (Figure 8).

The section for histomorphometry must be representative for the implant. As specimens taken from different levels of the implant might give different results, a standardized method for sectioning was used and all specimens for histology were taken at the same level of the implant (Figure 9). However, stereology is based on random sampling or unbiased measurements. Random sampling was not possible due to the relatively small sample size and unbiased measurements would require vertical section technique. It was not possible to fulfil these requirements. Therefore, the histomorphometric analysis should be regarded as a semiquantitative analysis in the present study.

Only one section was used from each implant for histomorphometry which might reduce the accuracy of the parameters. However, Vesterby et al. (342) found variance in bone density between sections (intersections variance) to be only 12%. If similar variation between

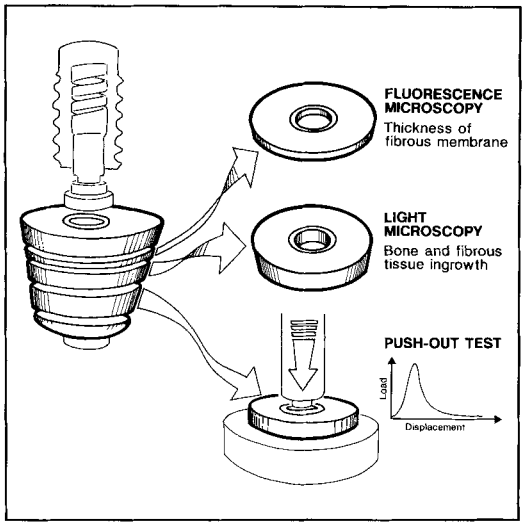


Figure 9. Standardized method for sectioning at right angles to the longitudinal axis of the implant. One section was used for measurement of membrane thickness, another section for quantitative analysis of bony ingrowth and a further section was used for the mechanical push-out test.

consecutive sections is assumed in the present study, this minor variation in bone ingrowth would not change the conclusions drawn.

Another problem that may influence measurements in histomorphometry is the thickness of the section. Section thickness of 100 μm is used by many investigators on bone ingrowth (88, 89, 316). The stained sections used for the present studies were ground to an approximately thickness of 50 μm but use of even thinner sections (10 μm) has been recommended (170) as the cellular layers in the section will overlap each other thus increasing the risk of misinterpretation since thicker sections might cause overestimation of bone ingrowth (170). Also variation on the obliquity of the section may contribute to minor errors (242).

Backscatter electron imaging-scanning electron microscopy (BEI-SEM) has recently been shown to give excellent results for quantitative analysis of bone ingrowth into porous coated implants (289). In this study, histomorphometry on ground stained sections of 100 μm thickness was compared with the BEI-SEM technique where backscattered electrons from only the superficial 1 to 5 μm of the specimen are emitted (160). The fraction of bone ingrowth was very comparable (correlation coefficient 0.96) using the two methods (289). These results suggest that histomorphometry on stained sections of 100 μm thickness does not overestimate bone ingrowth compared with a method including only the superficial 1 to 5 μm of the surface.

We used 100 x magnification for ingrowth patterns and 160 x for bone volume (gap healing). Using these resolution levels, a clear distinction between bone and fibrous tissue is possible (65). Regarding the metal-tissue interface, 100 x magnification may show intimate contact between bone and implant, but the real nature of the interface including the oxide layer on one side and biomolecules (molecular level) on the other side requires electron microscopic studies and specially prepared sections. Such studies have been performed (11, 203, 317).

Fluorescence microscopy. Fluorochromes were used as intravital markers for bone formation. These compounds are incorporated in the mineralizing surfaces during the time they are present in the blood circulation (115). The dogs were double labelled with tetracycline in all studies (10 and 3 days before termination). The only exception was in study VIII, where tetracycline was given 2 months before termination and calcein was given 5 days before termination to localize and differentiate the mineralizing surfaces at the two time periods.

The use of 100–150-μm thick sections for fluorescence histomorphometry may result in superimposed structures which might reduce the sensitivity of the evaluation. It was difficult to fulfill the requirement for thin sections for fluorescence microscopy as these sections were cut directly on the saw and variations of ± 25 μm was usual. Evaluation of these sections, however, was possible as superficially labelled bone could be differentiated from lower placed labelled bone by focusing on the surface to be measured which at least eliminates some of the error caused by differences in thickness.

Fluorescence microscopy seems to be less suitable for assessment of bone ingrowth as compared with evaluation of bone ingrowth on ground stained sections. Values obtained from mineralizing surfaces in contact with the implant surface cannot be used for comparison with those of other studies evaluating bone ingrowth on ground stained sections as the technique does not directly represent the amount of bone tissue in contact with the implant at termination. In study I both techniques were employed and comparisons were made between histomorphometry on ground stained sections (50 μm thick) and mineralizing surfaces obtained by fluorescence microscopy (150 μm thick). Despite a poor correlation, most tendencies were demonstrated using the two methods for evaluation of bone ingrowth except one comparison (HA-coated implant in press-fit versus gap) where no significant differences were found using fluorescent microscopy. However, mineralizing surfaces represent the relative differences thus reflecting the amount of newly formed bone at the time

of labelling. In other words, the host bone reaction between the compared groups in studies I, III, IV, and V differed so significantly that the relative differences in the amount of bone in contact with the implant surface was reflected using fluorescent microscopy.

In conclusion, mineralizing surfaces roughly parallelled results from push-out tests and did not overestimate differences in amount of bone ingrowth as compared with ground stained sections. Evaluation of bone ingrowth on the ground sections seems to be the most sensitive method, being capable of detecting smaller differences between compared groups.

Polarized microscopy. Fiber orientation in membranes surrounding unstable implants in study VII was studied on ground stained sections under transmitted polarized light microscopy equipped with a lambda filter. Differences between fiber orientation around Ti- and HA-coated implants could not be evaluated quantitatively as the analysis of fiber orientation was purely qualitative. The radiating orientation and the heavy appearance of fibers in membranes around HA-coated implants could be an optical phenomenon due to presence of precipitates of granulated material between fibers.

Investigator errors. To eliminate variation in estimates due to different observers (i.e. under- or overestimation of a parameter), the same observer performed all histomorphometric analyses. In addition, the histological evaluation was performed blindly and in a random sequence.

Reproducibility. The interindividual variation was calculated by double measurements with a 8-months interval on 12 randomly selected ground and stained sections (50 µm thickness) and involved estimating the accuracy of bone and fibrous tissue ingrowth and gap healing. These parameters were quantified blindly in a random sequence using linear intercept and point counting technique, respectively. Mean differences of 14% for gap healing , 13% for bone ingrowth and 8% for fibrous tissue were found in the 12 double-determinations and the mean coefficients of variance were 0.12, 0.14 and 0.10, respectively. Correlation coefficients of double determinations were 0.95, 0.95 and 0.99, respectively.

From these values it can be concluded that the observer remains relatively constant in ability to identify the parameters tested. The results should be compared to an interobserver error of about 10% for well defined features (181).

Histomorphometry and push-out test. The histomorphometric results roughly parallelled the push-out test as significant differences were demonstrated between the same groups compared except for four comparisons where histomorphometrical obtained differences were not confirmed by push-out results. Also "gap healing" corresponded positively with results from the push-out test. However, major differences were obtained using histomorphometry suggesting that parameters from this analysis are more sensitive than "shear strength."

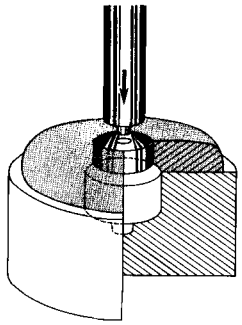


Figure 10. The push-out equipment. The specimen is placed on the metal platform with a central circular opening supporting the bone to within 500 µm of the interface. A 4-mm metal rod, with a concave tip fitting the screw-hole in the implant, was placed in the upper holding device for axial push-out testing of the implant from the surrounding bone. The load-deformation curve was obtained by an X-Y recorder as shown in Figure 1.

Mechanical testing

The purpose of the push-out test is to measure the strength of the interface between implant and surrounding tissue. However, the push-out equipment (Figure 10) has several critical points. An optimal mechanical test reflecting the forces occurring on a prosthesis does not exist as bending, shearing, and compressive forces will all act on the prosthesis in life. An alternative to push-out testing is torsional testing of cylindrical specimens which would generate pure shear at the bone implant interface (141, 278). The expressions "shear strength" and "shear stiffness" should therefore be interpreted with caution.

After completion of the series of present studies were finished, Harrigan et al. (141) published a paper on the usefulness of a push-out test as an indicator for interference shear strength using finite element analysis. The results showed that two considerations should be met if comparison of failure loads should be meaningful. First, the geometry of compared implants should be very similar and second, the experimental conditions should be well-controlled. The support boundary conditions seem to be particularly important in this respect.

Variation in the present experimental conditions was minimized by testing the specimens for each separate study on the same day using the same set-up.

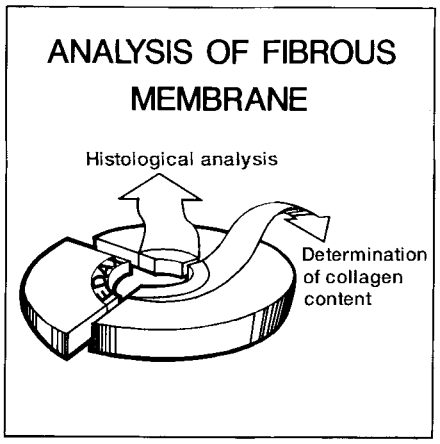


Figure 11. Standardized biopsy technique after removal of the implant. Biopsies were taken from the membrane using a stereomicroscope for histological analysis, collagen determination and elemental analysis (EDAX).

Concerning geometry, the surface structure was different for the HA and Ti implants. Ti implants had a more porous or rough surface whereas HA partly occupied the pores which reduced the surface area especially in the first studies (I, III–V). A rough surface finish has been shown to result in improved anchorage compared to smooth implants (69, 131, 312). Taking these facts into consideration, differences in geometry of the two implant types should result in a reduced fixation of the relatively smooth HA-coated implants as compared to the porous-coated implants. Thus, the push-out test would theoretically underestimate the fixation of HA-coated implants compared with Ti-coated implants.

For the last three studies a thinner HA-coating was used which as expected resulted in an even greater difference in fixation between Ti and HA-coated implants. Roughness measurements of implants revealed that only minor differences were present between Ti and HA-coated implants used in these studies (VI, VII, VIII).

The optimal difference between implant diameter and the hole to receive the implant during testing is problematic as a decreased distance between the implant and support ring would lead to stress concentration, whereas increased distance would decrease stress concentration (141). A recent report using finite element analysis on the push-out test concluded that the most critical parameter was the clearance of the hole in the supporting jig, clearance being recommended to be at least 0.7 mm (98).

Some authors use 150 μm clearance (89, 316) but the present studies used 500 μm clearance which is close to that recommended by Dhert et al. (98). Furthermore, histological analysis of implants after the push-out test showed that most implants had failed at the bone-implant interface using 500 μm clearance. The failure at testing in the present studies occurred predominantly at the bone-implant interface but small amounts of bone on both implant types were observed under the microscope in some specimens following push-out test. No failures of HA from metal substrate were observed during the push-out test. All HA-coated specimens from paper VIII were selected to quantify the amount of HA on specimens not subjected to push-out test, and results were compared with similar embedded specimens that were subjected to push-out tests then processed for later histological evaluation. The results indicated that the fracture during the push-out test did not occur at the HA-metal interface as the amount of HA was not reduced after the push-out test.

Another critical point is that mechanical testing is normally performed after the animal is killed and the specimens have been frozen. It is difficult to assess the effect of freezing on the bone-implant interface but the mechanical properties of trabecular bone do not change after freezing to –20 °C for 100 days (200). Even repeated thawing and freezing does not influence the mechanical properties of bone (200). No signs of initial cracks at the bone-implant interface were found during push-out tests suggesting that the freezing procedure did not influence the fixation of the implant. Alternatively, to avoid freezing, push-out tests could have been performed daily, but this would have induced errors due to daily variation in reproducing the set-up of push-out equipment.

In order to standardize the mechanical test an initial load of 2 N was used to define the contact position in all specimens.

Evaluation of fibrous membrane

Membranes from specimens used for the push-out test were isolated for histological analysis and determination of collagen content. The membranes (studies VI-VIII) were isolated from the surrounding bone under a dissecting stereomicroscope. The biopsy technique was standardized (Figure 11) using landmarks in the surrounding bone. Standardized biopsies for microanalysis (VII) were taken from the specimens used for fluorescence microscopy.

Hydroxyproline concentration. The hydroxyproline concentration was determined choliometrically a.m. Woessner (352) and the collagen concentration was calculated by multiplication of hydroxyproline concentration by 7.46 (19; Table 6). A methodological problem in

Table 6. Results from determination of collagen concentration (percentages) in membranes around Ti-coated and HA-coated implants. Mean *SEM*

Collagen concentration	Movement	
	500 µm (VI)	150 µm (VII)
TI implants	37 *8.8*	39 *5.3*
HA implants	57 *14*	43 *9.3*

determining collagen concentration was the presence of calcium/phosphate precipitations in the membranes around HA-coated implants and metal ions around Ti-implants (VII) which might contribute to a false increase in dry-weight of the membrane and thus a relatively lower concentration of collagen.

Electron microscopy (microanalysis). Both quantitative and qualitative chemical analyses were possible using the electron microscope for microanalysis. Analysis was qualitative with respect to presence/absence of metal or Ca-P ions in the membrane, but quantitative with respect to the amount of Ca and P in each particle analyzed. Quantitative analysis allowed a calculation of the Ca/P ratio in the particles which gave information on the chemical composition in membranes surrounding the implants (VII).

Histological analysis. In the histological analysis, fibrocartilaginous tissue was quantified using the point counting technique. Fibrocartilage was defined as presence of chondrocytes, fibrous connective tissue without chondrocytes accounting for the remaining tissue in the membrane. This definition of fibrocartilage, although a modification, seems to be the most reliable definition used for quantification of type of fibrous tissue.

CT-scanning

CT-scanning was used to evaluate the amount of juxta-articular bone loss after induction of chronic arthritis of the knee.

The precision of the scanning procedure used in the present model (I–V) was tested by performing six independent double-examinations of both knees at the epiphyseal level with complete repositioning between each examination (II).

The scans from the reproducibility test were analyzed blindly in a random sequence and included not only variations from the position of the scanner but also variations in the placement of region of interest (ROI) and variations in location of the distal limit of the femoral epiphysis (reference level). A mean difference of 0.2% was found in the 24 double-determinations and the mean coefficient of variance was 0.8%, values from the arthritic bone being greatest. Correlation coefficient of double determinations was 0.91 ($p < 0.0000$, n 24). The interindividual variation of bone density ranged from 7% to 15% between identical condyles, with greatest variation in the arthritic bone.

In addition to CT-scanning, histomorphometry (trabecular bone volume) and mechanical testing (indentation test) were performed to verify the degree of osteopenia (II).

Statistics

Mean and standard error of the mean (SEM) were calculated from all parameters. Statistical analysis was performed with student's paired and unpaired t-test. Differences were considered statistically significant when the p-value was less than 0.05. Analyses of variance for repeated measures were performed on push-out data to determine differences in presence/absence of HA-coating and stability (VI).

Results

Effect of a gap between bone and implant

In study I, the effect of HA was investigated when implants were surrounded by a gap compared with press-fit inserted implants. The observation period was 4 weeks and the material comprised six mature dogs. The gap model is shown in Figure 4.

The initial 1-mm gaps surrounding the implants were bridged by very limited amounts of immature woven bone around Ti implants whereas a great amount of newly formed bone filled the gap around HA-coated implants (Figure 12). Bone tissue was observed in direct contact with the HA implant surface and no interposed fibrous-tissue layer was present. In some areas a thin fibrous layer separated the Ti implant surfaces from the ingrown bone, but in most areas direct apposition of bone was noted.

A gap around Ti-coated implants resulted in a 65% reduced fixation compared with press-fit inserted Ti implants (Figure 13). In contrast, only slight reduction in fixation due to the gap was obtained using HA-coating. For these implants surrounded by a gap, the fixation of HA-coated implants was 120% increased compared with Ti implants and the corresponding value for shear stiffness was 425%. The HA-coating enhanced bone ingrowth also when inserted in press-fit (Figure 14). However, this enhancement was not confirmed by push-out test.

The greatest amount of bone ingrowth was found at the HA-coated implants inserted in press-fit which was increased compared with HA-coated implants surrounded by a gap, which again was greater than Ti implants in press-fit. The smallest amount of bone ingrowth was found at Ti implants surrounded by an initial gap (Figure 14).

Study IV also showed a greater amount of bone ingrowth on HA coated implants when surrounded by a gap even in presence of osteopenic host bone.

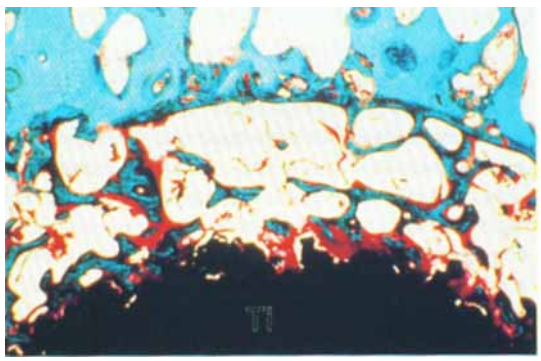


Figure 12a. Microphotograph from a Ti-coated implant initially surrounded by a 1-mm gap. Note the border of the drill hole and the limited amounts of bone (green) bridging the gap and fibrous tissue (red) separating some of the implant from the newly formed bone. Basic fuchsin and light green; original magnification x 25. Ti = titanium.

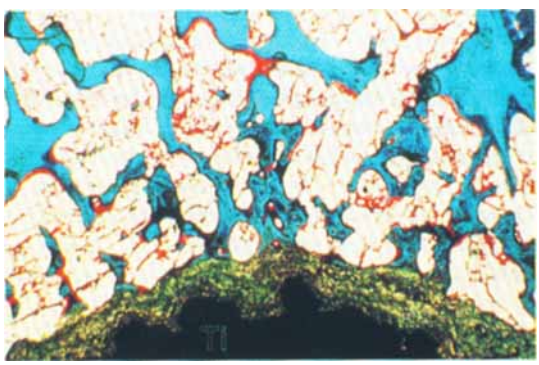


Figure 12b. Microphotograph from HA coated specimen initially surrounded by a 1-mm gap. Note the great amount of newly formed bone bridging the initial gap and absence of fibrous compared with the titanium coated implant in Figure 12a. Basic fuchsin and light green; original magnification x25. HA = hydroxyapatite, Ti = titanium alloy.

Effect of osteopenia on bone ingrowth

In study III, we used an experimental model with Carragheenin induced arthritic bone changes (309). Implants were inserted in tight press-fit for 4 weeks and the material comprised twelve mature dogs. Prior to surgery, CT scanning had verified a reduced bone density at the implantation site in the arthritic bone compared with control bone, this reduction amounting to 21 % (II). Following termination, the mechanical properties were verified to be weaker at the arthritic bone by the indentation test, and the trabecular bone volume was also shown to be reduced by histomorphometry.

At termination, gross capsular thickening, slight chronic synovial effusion, severe synovial thickening and muscular atrophy were observed in the arthritic knees. The articular cartilage was pale and fibrillated,

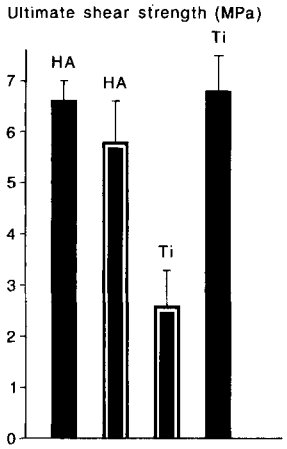


Figure 13. Results from the push-out test from gap/press-fit study. The line around the two bars in the middle illustrates implants surrounded by an initial gap. The two other bars represent implants inserted in press-fit. Mean (SEM), n=6. HA = hydroxyapatite, Ti = titanium.

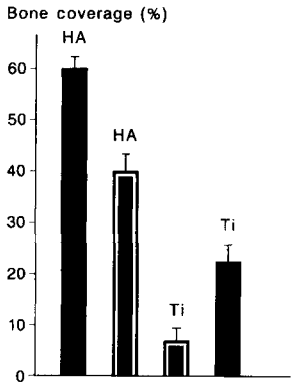


Figure 14. Results from histomorphometry on bone ingrowth into Ti and HA coated implants from the gap/press-fit study. The line around the two bars in the middle illustrates implants surrounded by an initial gap. The two other bars represent implants inserted in press-fit. Mean (SEM), n=6. HA = hydroxyapatite, Ti = titanium alloy.

and the articular surfaces were denuded of cartilage in areas of the patello-femoral groove and on the tibial plateaus.

Ti implants displayed several areas without direct bone-implant apposition, whereas bone tissue was in direct contact with the HA-coated implants and interposed fibrous tissue layer was present only sporadically. Mineralizing osteopenic bone at the surface of Ti implants was reduced by 20% ($p < 0.02$) compared with control bone. In HA-coated implants, however, there were only minor differences in mineralizing surfaces (MS) between osteopenic and control bone, but a comparison of HA- and Ti-coating in osteopenic bone showed a 50% increase in MS on the HA-coated implants ($p < 0.05$).

The anchorage of Ti-coated implants in osteopenic bone was significantly reduced compared with control bone ($p < 0.01$; Table 7). However, using HA-coated implants, no differences between osteopenic and control bone were found. In the control bone, the ultimate shear strength of Ti implants was significantly higher compared with that of HA-coated implants ($p < 0.01$) whereas no difference was found between HA and Ti implants in osteopenic bone.

Effect of bone grafting on bone ingrowth

Paper V evaluated cancellous allogeneic bone graft incorporation into porous coated implants and compared the fixation of Ti- and HA-coated implants with and without bone graft after a 6 week observation period. Twelve mature dogs comprised the material. The cancellous bone graft was taken from the proximal humerus from 12 other dogs, stored in sterile containers at –80 °C and subsequently milled into a homogeneous graft. In addition, the osteopenic model was also utilized. The CT-density was significantly reduced in the arthritic bone (right knee) as compared to the control bone (left knee) ($p < 0.01$). The bone graft model is shown in Figure 5.

In the non-grafted group variable amounts of immature woven bone and bone with lamellar structure was found to fill the 2-mm gap around the implants. Around HA-coated implants two zones of condensed bone structure were often present, one being at the implant interface and the other at the border of the drill hole. The condensed zone at the implant interface was not present around Ti-coated implants. No inflammatory cells or foreign body reaction was seen. The non-grafted Ti implants displayed several areas with interposed fibrous connective tissue, whereas bone tissue was in direct contact with the HA-coated implants with only sporadically interposed fibrous tissue layer present.

Table 7. Push-out values (MPa) for Ti-coated and HA-coated implants from Study III after 4 weeks in osteopenic and control bone (n 7). Mean *SEM*

Ultimate shear strength	Osteopenic bone		Control bone	
Ti implants	7.4	*0.22*	10.1	*0.6*
HA implants	7.7	*0.6*	7.5	*0.1*

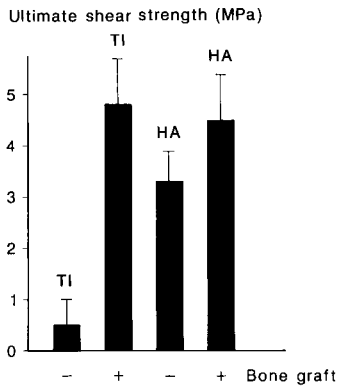


Figure 15. Results from the push-out test from bone graft study. Use of bone graft to fill in the defect is illustrated by +, whereas - indicates that bone graft was not used so leaving the implant surrounded by a 2 mm gap. Mean (SEM), n=7. HA = hydroxyapatite, Ti = titanium alloy.

The bone graft appeared to have been replaced by normal bone in direct contact with the implant. Small amounts of residual dead trabecular elements with empty osteocyte lacunae were detected in the grafted group. The mechanical parameters showed up to 900% enhanced fixation of grafted Ti-coated implants compared with that of non-grafted Ti-implants ($p < 0.001$) (Figure 15). However, HA-coating alone (without bone graft) was capable of enhancing the fixation to almost the same magnitude in 2 mm defects. Only a minor and non-significant additional increase was obtained when bone graft was used together with HA. No difference in implant fixation was found between osteopenic and control bone.

Effect of micromotion on bone ingrowth

The significance of relative movements between implant and surrounding bone was studied in papers VI and VII. In paper VI, movements of 500 µm were studied and in paper VII 150 µm movements were investigated. Mechanically stable implants functioned as controls in both studies. The observation period was 4 weeks. The micromotion device is shown in Figure 6.

In both studies, micromovements resulted in development of a fibrous membrane whereas bone ingrowth was obtained in mechanically stable implants (Figure 16). In addition, both studies demonstrated the development of islands of fibrocartilage around unstable HA-coated implants whereas the membrane consisted predominantly of connective tissue around unstable Ti implants (Figure 17). Collagen concentration was significantly higher in membranes around HA-coated implants as compared with membranes around Ti implants (VI).

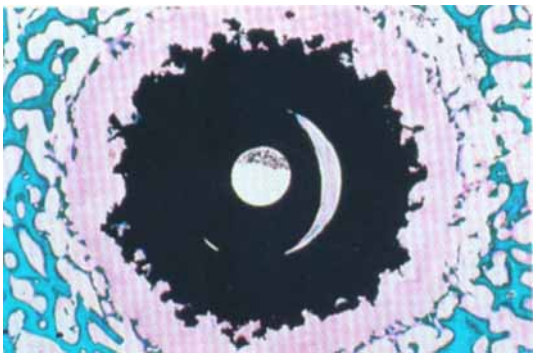


Figure 16A. Photomicrograph from an implant subjected to micromovements showing fibrous tissue membrane (red) separating the implant from the surrounding bone (green). Light green, basic fuchsin, grounded section, original magnification x6.

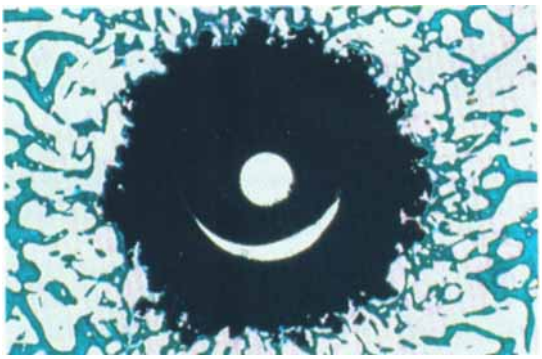


Figure 16B. Photomicrograph from a stable implant showing bone ingrowth across the initial gap and bone apposition on the implant. Light green, basic fuchsin, grounded section, original magnification x6.

500 µm movements (VI). Seven mature dogs comprised the material. Push-out testing showed that the shear strength of unstable Ti- and HA-implants was significantly reduced compared with the corresponding mechanically stable implants ($p < 0.01$) (Figure 18). However, shear strength values of unstable HA-coated implants were significantly greater than those of unstable Ti implants ($p < 0.01$), and were comparable to those of stable Ti implants. The greatest shear strength was obtained with stable HA-coated implants, which was three-fold increased compared with stable Ti implants ($p < 0.001$). Quantitative determination of bony ingrowth confirmed the findings of the mechanical test, except for the stronger anchorage of unstable HA implants compared with unstable Ti implants where no difference in bony ingrowth was found.

150 µm movements (VII). Fourteen mature dogs were used in this study. Results from the 500 µm study

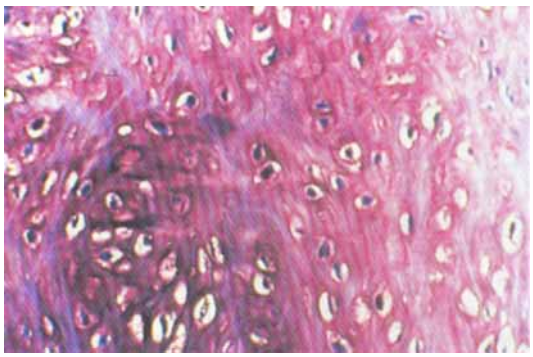


Figure 17A. Photomicrograph of membrane surrounding an unstable HA-coated implant showing fibrocartilage with chondrocytes in lacunae. Toluidine blue at pH 5, original magnification x250.

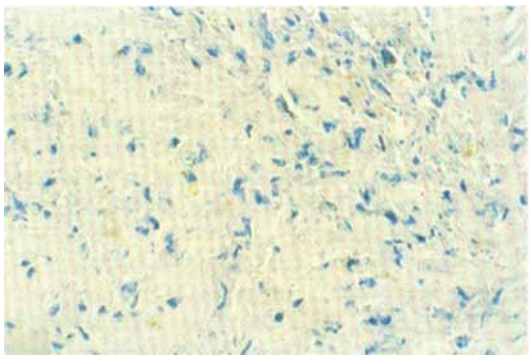


Figure 17B. Photomicrograph of membrane surrounding an unstable Ti-coated implant showing fibrous connective tissue. Toluidine blue at pH 5, original magnification x250.

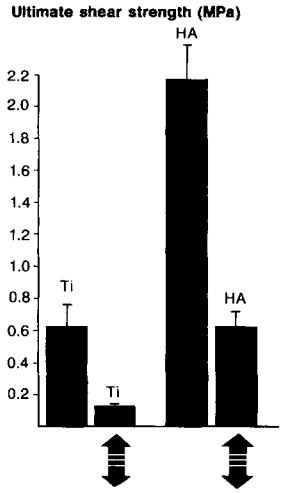


Figure 18. Results from the mechanical push-out test from the 500 µm movement study (VI). The arrows indicate unstable implants, the two other bars represent stable implants. Mean (SEM), n=7. HA = hydroxyapatite, Ti = titanium alloy.

regarding presence of fibrocartilage in membrane around unstable HA-coated implants, whereas fibrous connective tissue characterized the membrane around unstable Ti implants were again found in this 150 µm study. In addition, this study revealed a thinner membrane around unstable HA implants compared with unstable Ti implants. A radiating orientation of collagen fibers was found in the membrane around unstable HA-coated implants whereas a more random orientation was found in most membranes around Ti implants (Figure 19). Shear strength of unstable HA-coated implants was significantly greater than that of unstable

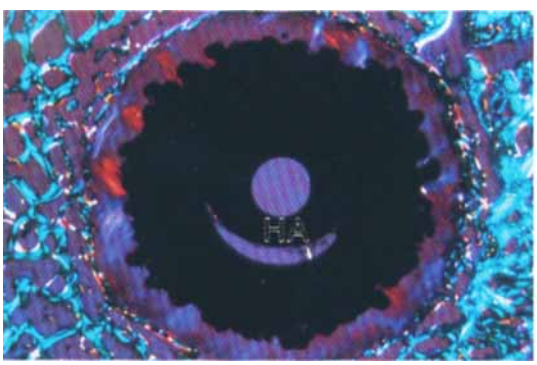


Figure 19A. Polarized light micrograph of an unstable *HA-coated implant,* showing the alignment of heavy bundles of collagenous fibers radiating fan-shaped from the HA-coated implant surface. The collagen fibers extend from the implant to a well-defined plate of condensed woven bone surrounding the membrane. (Polarized microscopy, light green and basic fuchsin, original magnification x6).

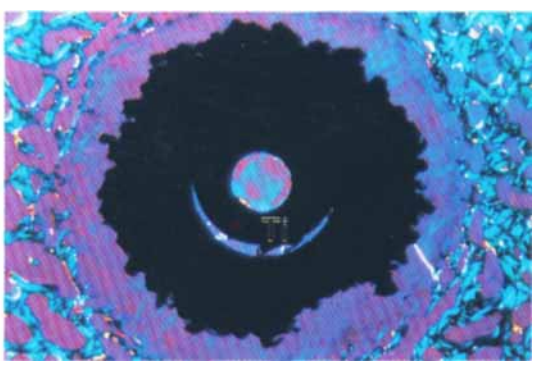


Figure 19B. Polarized microphotograph of an unstable *Ti implant* showing a more random orientation of thin collagenous fibers compared with the HA coated implant in Figure 18a. Also note the thicker membrane and a thinner condensed plate of bone surrounding the membrane compared with Figure 18a. (Polarized microscopy, light green and basic fuchsin, original magnification x6).

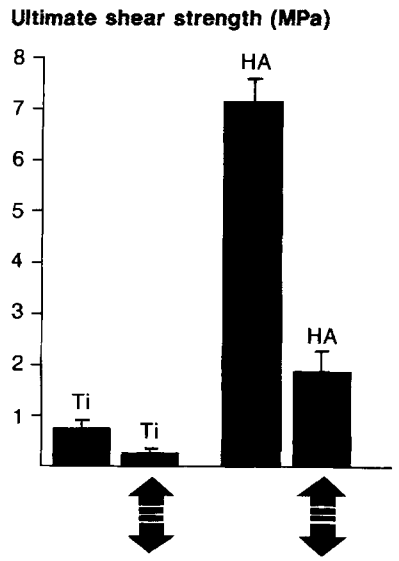


Figure 20. Results from the mechanical push-out test from the 150-μm movement study (VII). The arrows indicate unstable implants, the two other bars represent stable implants. Mean (SEM), n=7. HA = hydroxyapatite, Ti = titanium alloy.

Ti implants ($p < 0.001$) and also greater than those of stable Ti implants ($p < 0.05$; Figure 20). The greatest shear strength was obtained by stable HA-coated implants which was ten-fold increased compared with stable Ti implants ($p < 1x10^{-8}$). No significant difference was demonstrated between the amount of bone apposition on unstable HA and stable Ti implants. The gap-healing capacity around stable HA-coated implants increased towards the HA surface and was significantly greater than that of Ti implants.

Effect of immobilization versus continuous loading on bone ingrowth.

In the previous two studies, a fibrocartilaginous membrane was evident around HA-coated implants subjected to micromovements for 4 weeks, whereas fibrous connective tissue predominated around Ti implants. In study VIII, the consequence of subsequent immobilization of Ti and HA-coated implants surrounded by a motion-induced fibrous membrane was studied and results compared with similar implants where continuous load was permitted. All implants were initially subjected to 150-μm movements and after 4 weeks (when a fibrous membrane had developed around the implants) half of the implants were unloaded to prevent further micromovements and the other half were allowed continuous load. Fourteen mature dogs comprised the material and the observation time was 16 weeks.

Histological analysis of implants with continuous load for 16 weeks showed bone tissue had replaced the membrane around HA-coated implants whereas a fibrous membrane was still present around Ti implants subjected to similar mechanical conditions (Figure 21).

The immobilized implants were surrounded by bone tissue up to the implant surfaces irrespective of type of coating.

Push-out testing of continuously loaded implants showed inferior fixation of Ti implants compared with HA-coated implants ($p < 0.001$). Immobilization of Ti implants resulted in 330% stronger fixation compared with continuously loaded Ti implants ($p < 0.01$). Immobilization of HA implants tended to increase the fixation by 40% but this result did not reach significance. The anchorage of immobilized Ti implants was 20% stronger than HA-coated implants but again statistical significance was not reached. However, the amount of

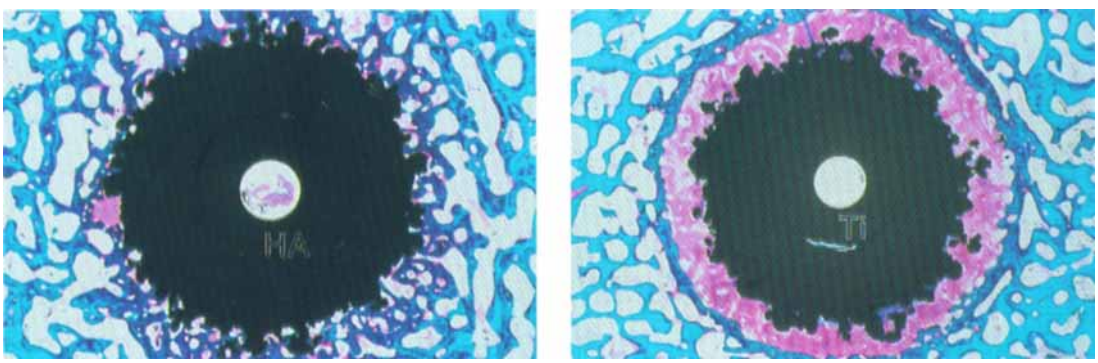


Figure 21. Similar implants as shown in Figure 19 after further 12 weeks with continuous loadin a HA-coated implant (left) and Ti-coated implant (right). Note that bone has replaced the membrane and filled the gap between bone and HA coated implant (left) whereas a fibrous membrane is still present around the Ti implant (right). Around the periphery of the fibrous membrane (right) a plate of condensed lamellar bone was found surrounding the membrane concentrically to the implant surface. Light microscopy, light green and basic fuchsin, original magnification x6.

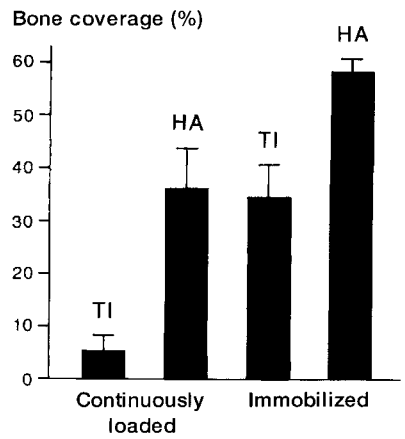


Figure 22. Results from histomorphometry on bony ingrowth into continuously loaded and immobilized implants 16 weeks postimplantation. The immobilized implants were initially subjected to micromovements for 4 weeks. Mean (SEM), (n=7). Ti = titanium alloy coating. HA = hydroxyapatite coating.

bone ingrowth was significantly greater into immobilized HA-coated implants compared with Ti implants (Figure 22).

Effect of load versus "non-loading" of stable implants

Dynamic loading (weight bearing) on HA-coated implants increased the amount of bone ingrowth and implant fixation which was three-fold greater compared with completely unloaded implants (VI, VII). No effect of weight bearing was found using Ti-coated implants (Figure 24).

Effect of HA-coating on bone ingrowth

The effect of HA-coating was tested in all studies described above. HA-coating had a positive effect on the implant anchorage both under stable unloaded conditions (I, III, IV, V), stable loaded conditions (VI, VII) and under unstable mechanical conditions (VI, VII, VIII). The HA-coating yielded superior effect on bone ingrowth compared to Ti in situations where the implant was surrounded by a gap (I, IV, V) and when inserted in press-fit even in osteopenic host bone (I, III). Gaps of 1 mm and 2 mm around the implant (I, IV, V) were bridged by bone around HA implants whereas only small amounts of bone filled the gap around Ti implants. During experimental osteopenic conditions, the anchorage of Ti implants was weakened compared with control bone; this weakening was not found when HA-coating was used. Allogeneic bone graft enhanced the anchorage of both Ti- and HA-coating, but HA-coating alone without bone graft offered virtually almost the same improvement in anchorage in 2-mm defects (V). During unstable mechanical conditions, HA-coating modified the fibrous membrane around the implant as evidenced by the presence of fibrocartilage, higher collagen concentration, radiating orientation of collagen fibers and a thinner membrane as compared with Ti- coated implants. In a longer-term study (16 weeks), the membrane around HA implants was found to be replaced by bone whereas the membrane around Ti implants persisted after 16 weeks (VIII).

Discussion

Factors affecting bone ingrowth

The ultimate purpose of implant fixation is to obtain a life long anchorage of the implant to the skeleton. Many factors contribute to the fixation of the non-cemented implant (Figure 23) and long term success after total joint arthroplasty (9, 281). These factors can be subdivided in relation to

- implant design
- status of host bone bed
- mechanical stabilization and loading conditions
- adjuvant therapies
- remodeling of periprosthetic bone

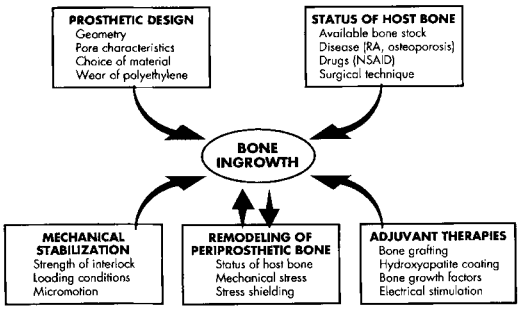


Figure 23. Factors affecting bone ingrowth and fixation of non-cemented implants (modified after Spector; 281).

Implant design

The design of the implant may vary with respect to

- choice of material
- geometry
- surface morphology

Choice of material

The choice of both bulk and coating material types is important because the implant's biocompatibility, corrosive resistance and mechanical properties are important factors for implant fixation.

Different types of materials have been used clinically as coatings. These include metals, ceramics, and composites (106, 138, 285, 292).

Metals. Metallic coatings are the most commonly used for clinical application and the fixation between different metals used for implantation in bone has recently been compared (170). It was demonstrated that fixation of c.p. Ti was superior to that of Vitallium, Ti-6Al-4V and stainless steel. The Ti-oxide layer that inevitably covers a c.p. Ti surface (174) is also present on Ti alloy surfaces (194). However, the oxide layer on the alloyed Ti also contains aluminum and vanadium which may be responsible for different tissue reactions (170). However, Linder demonstrated no differences in tissue reaction between c.p. Ti and Ti alloy at light- and electron microscopic level in rabbits (202, 205).

C.p. Ti has been used clinically as oral implant screws with a success rate of 90% after 15 years (13). However, the favorable mechanical properties of Ti alloy (Ti-6Al-4V) compared to c.p. Ti have been the motivation for preferring Ti alloy for load bearing prosthetic components (350) which currently constitute more than one third of all manufactured arthroplasties. Ti alloy prostheses with c.p. porous coating is now available.

Metal ion release from c.p. Ti as evidenced by blackening of the tissue around the implants has been reported (12). Also the use of Ti-6Al-4V has in addition to leakage of Ti resulted in leakage of Al and V ions. Aluminum, which was found in the lungs of baboons with Ti-alloy implants in bone tissue, is known to be neurologically toxic, but the brain tissue was not examined in this study (354). In the present study (VII), microanalysis demonstrated that Ti, Al and V containing particles were present around Ti-alloy implants, which was not surprising as in vitro and in vivo (2) studies have documented release of metal ions from Ti-6Al-4V alloy implants. An interesting finding was that HA-coating prevented or at least reduced the release of metal ions from the metal substrate, this being in agreement with the findings of Ducheyne and Healy (101).

Disagreement exists about the influence of Ti on surrounding tissues. In rabbits, Albrektsson and Jacobsen (12) have shown that c.p. Ti is highly biocompatible and that calcification of bone tissue occurs as close as 20 nm from the Ti surface. Linder (202, 205) demonstrated similar findings on Ti-alloy implants using the mechanical removal technique. However, a dose dependent increase in prostaglandin E_2 (PGE_2) release was demonstrated when Ti-Al-V particles were added to cell cultures (127) suggesting an adverse reaction to

Ti alloy particles but c.p. Ti was not tested in this particular study. We have found no similar studies on HA particles. However, the suggested adverse reactions described by Goldring et al. (127) might explain the difference in morphology of membranes around Ti and HA-coated implants in studies VI and VII.

Ceramics. Coating with biologically active materials (i.e. glass ceramics, calcium phosphate ceramics) has been developed and such coatings have been shown to be fixed by "direct bone bonding" resulting in a high interfacial strength (93). HA-coating is an example on this mode of fixation. In the present studies (I, IV-VIII) it was demonstrated that HA-coating was superior to Ti alloy, and in some of the studies no fibrous tissue at all was demonstrated on the HA-surface, whereas in other studies small amounts of fibrous tissue were observed. An interesting finding was that bone grows directly on the HA surface after 4 weeks (VII) which also was demonstrated on the Ti surface after 16 weeks (VIII).

Composites. Biomechanically, composites of polyethylene and polysulfone coatings (210, 229, 284, 285) are interesting because the modulus of elasticity of the implant can be changed to approximate that of bone this being desirable to avoid stress shielding (285). Composites of different types of materials are also used to optimize implant fixation. For example, metal composite prostheses where Ti alloy is used as the core owing to its high fatigue strength while c.p. Ti or HA is coated onto the area where bone ingrowth is wanted owing to their higher biocompatibility.

Recently, a new polymer "Polyactive" has been shown to bond to bone and might be an interesting material for future bone-implant surgery (340).

Wear of polyethylene. Wear debris of polyethylene should also be discussed in "choice of material" because it seems to be a serious problem in endoprosthetic surgery as this may govern the long-term outcome of total joint replacement (197). The wear rate has been reported to be 2.55 mm after a 10 year period (119). Polyethylene particles have been demonstrated at the interface around the femoral component in cemented and non-cemented THR and shown experimentally to induce loosening of a stable cemented interface (162). Polyethylene has been shown to be associated with histiocytic granuloma and focal osteolysis around the prosthetic component (63, 129, 212). Recently, zicronia and alumina femoral heads have been developed to reduce the wear rate and friction coefficient against polyethylene (271).

Geometry of implant

The available hip and knee prosthetic systems include a wide variety of material types, geometric designs and surface morphology, all factors which are determinative for the primary stability of the implant as well as long-term outcome (65).

New hip prosthetic designs (anatomic) with curved stems were generally designed to ensure optimal contact with the host bone and primary stabilization of the prosthesis but the effect of straight/curved stems is still a matter of debate. Bechtold et al. compared the initial stability of a long curved stem (BIAS), a short straight stem (Harris-Galante), and a short curved stem (PCA) (30). Both rotation and permanent shift were smallest for the long curved prosthesis and greatest for the short curved prosthesis. These studies support the importance of geometry of the implant for biological fixation, as mechanical stabilization is obtainable by some designs but not others.

The effect of a collar on the femoral component is also a matter of debate because the collar might contact the femoral neck and thus inhibit the implant from obtaining the desired press-fit in the femur (347). In the author's opinion, it is difficult to obtain optimal contact between the collar and the calcar femorale (300), this being necessary if stress shielding should be reduced by loading the femoral neck with a collar.

Regarding the acetabular component there seems to be general agreement that the shape should be hemispherical because this design reduces the amount of bone to be removed and allows retention of some of the subchondral bone plate to sustain the applied loads. Threaded cups have been shown to be less stable than porous coated cups (154, 326) and result in large gaps between bone and implant (269). Snorrason et al. (276, 277) showed by roentgen stereophotogrammetric analysis (RSA) that threaded cups migrated five- to ten-fold more than porous coated press-fit cups fixed with screws.

The effect of screws and pegs on stabilization of the tibial component in total knee replacement has been studied extensively in dogs and has shown significant reduction in micromotion (18,286). These findings have been confirmed in vitro (343) and by clinical RSA studies (5, 7, 226).

Also the long-term outcome after THR depends on the geometry of the prosthesis. In a clinical study of primary cementless THR it was shown that the use of larger stems (>13.5 mm) resulted in a significant increase in proximal bone resorption (stress shielding) as compared with smaller stem sizes, probably due to differences in elastic modulus (105).

Surface morphology

The morphology of non-cemented prosthetic surfaces may vary, and types include smooth, fenestrated, tex-

tured and porous coated surfaces. Another variable is location and length of porous coverage.

Smooth implants, also termed "press-fit" implants are fixed to the skeleton by bone apposition with intervening of fibrous tissue resulting in a relatively low interface strength. Smooth surfaced tibial components have been demonstrated to result in a high failure rate in total knee arthroplasty and have not been recommended for non-cemented use (222).

Textured and fenestrated implants. The term "macro-interlock" is used for textured and fenestrated implants which are fixed to the skeleton in the same manner as the smooth implants but the interface strength may be high depending on the thickness of the intervening fibrous tissue layer. The interlock obtained by cementation technique yields the best fixation as demonstrated by roentgen stereophotogrammetric analysis (6, 220, 261).

Porous coating may lead to "microinterlocking" by bone ingrowth (281), also termed biological fixation (282). Great variation in the amount and extent of bone ingrowth may occur as animal studies generally have shown high percentage of bone ingrowth, whereas retrieved prostheses from human patients have shown inferior bone ingrowth (81, 86, 314). Experience with fully porous coated femoral components has revealed problems with stress shielding leading to non-anatomical bone remodeling around the proximal part of the prosthesis (330). To overcome this problem, different modes of fixation have been combined in the same implant e.g. if the porous coating is limited to the proximal part of the femoral component in THR, bone ingrowth would occur in this area resulting in stress distribution at the proximal part of the prosthesis whereas the smooth surface distally would have an interface with a weaker bonding thus tending to leave the stress to the proximal part of the femur.

The pore dimensions should theoretically be larger than the dimensions of the elements comprising bone (osteoblast 20 μm in length, capillaries 10 μm in diameter, and extracellular elements; 281). Several studies have been performed to determine the optimal pore size for bone ingrowth. Bobyn et al. suggested that a pore size between 50 and 400 μm provided the optimal amount of bone ingrowth in the shortest time period, whereas larger pore size (400–800 μm) resulted in inferior fixation (47). Another study on intramedullary implants (77) showed a decrease in fixation with increasing pore diameter from 175 to 325 μm. In the present studies (I, III–V), it should have been expected that the fixation of Ti implants was superior to those of fibrous anchored HA-coated implants since the pore size was diminished by HA-coating thus reducing the surface area. Consequently, the positive effect of HA-coating on implant fixation might have been even stronger than demonstrated had the pore size had been equal on Ti- and HA-coated implants.

Pore size has been shown to be important also for soft tissue ingrowth. Laberge et al. (191) demonstrated that vascularized fibrous membranes developed within and around large pore sized implants (900 μm) whereas a non-vascularized fibrous membrane surrounded the smaller pore sized implants (300 μm). These authors suggested that a large pore size seems to be necessary for achieving soft tissue ingrowth and mechanical attachment. In papers VI and VII it was demonstrated that a pore size ranging between 300 and 1000 μm resulted in a relatively strong implant anchorage in soft tissue when HA-coating was used compared with soft tissue anchorage of Ti implants with a larger pore size.

Different types of coating also seem to influence the amount of bone ingrowth. Turner et al. showed that fiber metal coated (pore size 247 μm) femoral components in the dog obtained more bone ingrowth than bead coated (pore size 297 μm) components (331).

Generally, a porous surface coating may be advantageous from a mechanical point of view since stress distribution may be improved (69, 275, 312) as compared with smooth surfaces. Also the primary fixation might theoretically be stronger as compared with a smooth surfaced prosthesis.

Status of host bone bed

Host bone factors can be separated into

- Available bone stock
- Disease (rheumatoid arthritis, osteoporosis)
- Drugs
- Surgical technique

Available bone stock

The quantity of bone ingrowth into porous coated implants also depends on available bone stock and the interference fit obtained with the surrounding bone (9, 62, 68, 143, 265).

In the present study it was shown that a gap of 1 mm around the implant reduced the fixation of Ti implants by two-thirds compared with implants inserted in press-fit (Figure 13). These findings are in agreement with those of others (68, 265). Carlsson et al. (68) studied the importance of surgical fit between implant and bone and found that even minor gaps (0.35 mm) around stable smooth c.p. Ti cylinders were not bridged by bone and that the critical gap was close to zero.

In conclusion, optimal contact between bone and implant is very important for the success of bone ingrowth and one possibility to improve the fixation of non-cemented implants is to optimize contact areas at the bone-implant interface during implantation. Latest computerized aided reamers (surgical robotics) have been produced to obtain a more precise fit and thereby initial stability of the implant (26).

Disease (rheumatoid arthritis, osteoporosis)

The biological response to the implant depends, among other factors, on the status of the host bone bed at the time of implantation. The bone bed can be osteopenic due to disuse, rheumatoid arthritis or osteoporosis. Only few quantitative data are available on the ingrowth capability of osteopenic bone (214, 223, 263).

We used an experimental model with arthritis-induced bone changes resulting in osteopenia (II, III–V). A weakened fixation of Ti implants in osteopenic bone was demonstrated suggesting that bone quality can be a limiting factor for biological fixation. These results are in agreement with two other experimental studies using ovariectomized dogs (214) and old dogs (223) but does not agree with a steroid induced osteopenic model in rabbits where bone ingrowth was not reduced (263).

Our results are also in agreement with a clinical study on osseointegration of c.p. Ti screws (204) which showed inferior bone contact with most screws implanted in patients with rheumatoid arthritis compared with osteoarthritic patients with good bone quality.

If the results mentioned above could be extrapolated to weight bearing human joint prostheses, they would suggest inferior results with metal porous coated non-cemented prostheses used for patients with an osteopenic host bone bed.

Drugs

Non steroid anti-inflammatory drugs (NSAID) are used by many patients with destructive joint disease and these have been demonstrated to reduce fixation and the amount of bone ingrowth into Co-Cr porous coated transcortical implants (209, 328). Disodium etidrinate (EHDP) which is effective for heterotopic ossification associated with total hip arthroplasty likewise inhibits bone ingrowth into porous Ti fiber metal. (256) Similarly, steroids are known to result in bone loss (113, 263) and might reduce fixation of the implant. Methotrexate is being increasingly used in the treatment of rheumatoid arthritis and has recently been shown to adversely affect biological attachment of porous coated and HA-coated implants (208).

Other agents such as radiation therapy are reported to inhibit bone ingrowth up to 8 weeks after implantation (293).

Surgical technique

Surgical technique may result in various degrees of interruption of the blood supply and bone necrosis during cutting and reaming (8). Toksvig-Larsen et al. found the cutting procedure for knee arthroplasty to generate heat above the critical temperature for bone necrosis (321, 323, 324). However, careful surgical technique can result in significant reduction of temperature (109). Recently, an internally cooled saw blade used for cutting tibial bone for total knee replacement was shown to result in a stiffer bone-implant interface as evaluated by RSA (325).

The cutting procedure may also result in lack of optimal flatness after bone cutting for non- cemented tibial components (320, 322) . In these studies it was calculated that the prosthesis will rest on only 1–2% of the surface area immediately after insertion. Other authors have emphasized the lack of direct apposition of implant to bone in the clinical situation (43, 106, 269).

Studies I, III–V demonstrated that the quantity of bone ingrowth into porous coated implants depends on the interference fit obtained with the surrounding bone and that gaps result in inferior bone ingrowth when Ti implants were used. However, the demand on surgical technique appears to be lessened when HA-coating is used because the latter eliminated the negative influence of a gap between bone implant (I, IV, V, VI, VII). However, every effort should of cause still be made to achieve optimal press-fit and as rigid an initial fixation as possible.

A new concept of "guided tissue regeneration" involving an occlusive teflon membrane has recently been shown to enhance gap healing around Ti-implants in the alveolar ridge in monkeys (132, 345).

Mechanical stabilization and loading conditions

Mechanical stabilization can be separated into
- Initial mechanical stability
- Loading conditions
- Micromotion and fibrous membrane formation

Initial mechanical stability (strength of interlock)

Obtaining rigid initial stability of the implant seems to be one of the major problems in non-cemented endo-

prosthetic surgery and depends initially on the strength of mechanical interlock between implant and bone achieved during implantation.

Factors of importance for initial stability of the implant include (221):

- Strength of the local bone.
- Surface area of interface.
- Interlock achieved during implantation..
- Forces acting on the implant

In general, if the force on the implant becomes greater than the strength of the mechanical interlock at the bone-implant interface, implant motion will occur until mechanical interlock of new bone ingrowth has been established.

Several investigations have been performed to study the stability of hip and knee prostheses immediately after implantation and there is agreement that relative movement between implant and bone occurs over the range 100–600 µm (49, 56, 273, 286, 341, 343). Even when using rigid fixation with screws and pegs, differences in elasticity between bone and the metallic porous material may result in tangential displacement of 150 µm at the periphery of tibial trays (291). In contrast, cemented prostheses appear to be more stable (261).

Initial stability of the implant was shown to be a requirement for achieving bone ingrowth (VI, VII, VIII) this being supported by other studies (21, 60, 61, 100, 110, 148, 248, 249, 266, 336, 337). The current studies demonstrated that micromovements as small as 150 µm during each gait cycle result in the development of a fibrous membrane, whereas bone ingrowth occurs around mechanically stable implants (Figure 16; VI, VII, VIII).

The threshold of implant motion allowing bone ingrowth is still unknown. A recent dog study showed bone ingrowth and remodeling into non-cemented femoral components in THA despite an initial implant motion of 56 µm (356). Burke et al. (55) supported our results using another model with controlled movements of 150 µm for 8 hours a day which prevented bone ingrowth and resulted in a dense fibrous tissue layer surrounding the implants. Similar implants with 20 µm movements achieved bone ingrowth indicating that the threshold for bone ingrowth is between 20 µm and 150 µm movement. These findings seem to be in agreement with Sumner et al. (291) who showed that bone ingrowth occurs close to the fixation pegs in Ti fiber metal coated tibial components, whereas minor amounts of bone ingrowth occur at more peripheral sites of the prosthesis probably due to tangential displacement in the range of 150 µm at the periphery of the tibial tray (224, 335, 355).

Table 8. Ultimate shear strength (MPa) of unstable Ti-coated and HA-coated implants (n 7) with different observation time and range of motion. Mean *SEM*

Weeks observation	4 (VI)	4 (VII)	16 (VIII)
Range of motion (µm)	500	150	150
TI implants	0.12 *0.01*	0.26 *0.07*	1.8 *0.8*
HA implants	0.63 *0.1*	1.85 *0.4*	4.6 *1.0*

Thus, there seems to be a relationship between the magnitude of bone implant-motion and type of interfacial tissue developed. It is therefore of interest to look at the effect of different amounts of movement on implant fixation (Table 8). An increased fixation strength was obtained with decreased range of motion (500 µm to 150 µm) for both HA and Ti implants, and a further increase in fixation when the observation time was extended from 4 weeks to 16 weeks (VI, VII, VIII). Comparison between the fixation strength of continuously loaded Ti implants after a 16-week observation period (1.8 MPa; VIII) and that of HA-coated implants from the 4 weeks study (1.85 MPa; VII) indicates that fixation of fibrous anchored HA implants is obtained in 1/4 of the time required for the equal fixation of implants without HA-coating.

In conclusion, if the aim is bony ingrowth, every effort should be made to achieve as rigid an initial fixation as possible in order to avoid relative motion between bone and implant which otherwise results in fibrous membrane formation (VI, VII, VIII).

Two stage surgery. To ensure primary stability for obtaining secondary stability before load is applied, two stage surgery has been advocated for oral implants (50). Brånemark unloaded dental implants during the first 3 months to ensure osseointegration before load was applied (50). Using this technique in the mandible, a success rate of 90% after 15 years has been achieved (13). Two stage surgery has also been used experimentally in orthopaedic studies where the implants were unloaded initially for 3 months before actual loading was applied (4). After 9–12 months of load the c.p. Ti implants were shown to be anchored in bone without interposition of soft tissues. In the orthopaedic field, however, is seems problematic to perform joint replacements using two stage procedures as this would necessitate two intraarticular operations so creating the risk of infection and thereby loss of implant, as stated by the authors themselves (4).

Röstlund et al. (258) developed an experimental dynamically loaded femoro-patellar joint in the rabbit. After 3 months, 60% of the c.p. Ti screw used for

anchorage of the prosthesis was covered by bone. They therefore concluded that osseointegration may be obtained in a one stage procedure in this model where the load transfer is favorable.

Loading conditions

Protected weight bearing in the postoperative period has been a matter of debate for many years. Protected weight bearing might reduce the load on the prosthetic component and thereby lower the risk of micromovements between bone and implant. However, the optimum duration of protected weight bearing remains to be elucidated. According to the present studies this period might be shortened because HA-coating appears to accelerate bone ingrowth during stable mechanical conditions or replace a motion-induced fibrous membrane by bone (VI, VII, VIII). Thus, HA-coating may be expected to reduce the duration for secondary fixation and thereby reduce the protected weight bearing period.

The duration of a stable interface obtained by the initial interlock between implant and bone is very short. Burke et al. showed that the primary good stability provided by press-fit insertion of porous coated implants had deteriorated significantly 2–3 days after load application, which is too short a time to obtain bone ingrowth (55).

It is difficult to give exact time periods for protected weight bearing, but Oonishi et al. suggested that HA-coated implants obtained reliable fixation for full weight bearing after 2–4 weeks, sand-blasted Ti implants after 3–8 weeks and Ti-alloy porous-coated implants after 5–7 weeks (235).

The issue of load protection is controversial since significant loads on a femoral component in THA have been shown to occur even during active exercises in bed, measured loads being in the range of those produced during walking (34, 35). In this study, normal walking resulted in loads averaging 277% of body weight (BW), lifting the straight leg in bed resulted in 150% BW and when the patient worked against resistance the load increased up to 270% BW (35). According to these results it is questionable whether sufficient load protection of the hip joint can be accomplished.

Loaded versus unloaded implants. In study VII it was demonstrated that bone ingrowth could occur into loaded but stable implants even in the presence of an initial gap around the implant. Dynamic load was even shown to increase the amount of bone ingrowth, being three-fold greater compared with completely unloaded implants (VI; Figure 24). The stronger fixation of loaded HA implants is in agreement with Turner et al. (331)

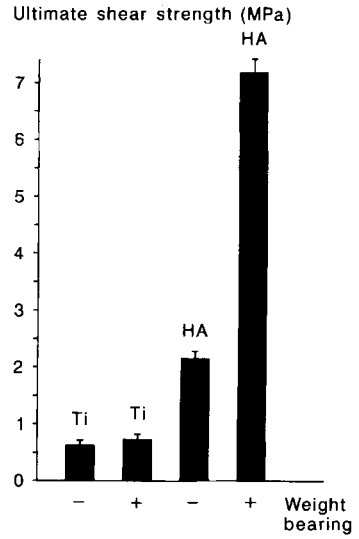


Figure 24. Ultimate shear strength of stable HA- and Ti-coated implants with (+) and without (–) weight bearing after 4 weeks. Mean (SEM), n=7.

who suggested that underloading (stress shielding) results in inferior bone ingrowth and cortical resorption around the implant. Jasty and Harris (168) also showed the importance of loads on rigidly fixed acetabular components as unloaded components showed inferior bone ingrowth compared with loaded components. This is in agreement with Wolff's law stating that bone adapts to functional demands by remodeling to reflect the distribution of effective stresses (353).

Fixation of an implant seems to depend on, among other factors, the loading conditions applied on the implant. Three different loading situations could be compared in the present studies (VI, VII): the stable unloaded situation; the stable loaded situation; and the unstable situation.

The *loaded* stable situation obtained the best anchorage and the greatest amount of bone ingrowth (VI, VII) as compared with the unloaded situation. These results suggest that some kind of weight bearing enhances bony anchorage of the implant (VI,VII). On the other hand, "too much" weight bearing will induce a negative effect on implant fixation because the amount of micromotion will surpass the limit compatible with bone ingrowth (VI, VII). So far, the limit between enhancement of bone ingrowth due to implant loading and inhibition of bone ingrowth due to "overloading" (micromovements) remains unknown, but is definitively less than 150 μm movement (VII).

One explanation for the lack of effect of weight bearing on stable Ti implants (Figure 24) might be delayed

gap dealing (VI, VII) as compared with HA implants. This delay in bone ingrowth means that only minor amounts of bone were present at the time of weight bearing and thus little bone to respond to the mechanical stress applied on the implant. In other words, a positive effect of early weight bearing is only obtainable if continuity between surrounding bone and implant is achieved at an early phase after implantation. Another explanation might be that applied stress on HA-coated implants results in increased dissolution of HA which, according to Beight et al. (32), would stimulate additional bone ingrowth.

Micromotion and fibrous membrane formation

Bone or fibrous tissue ingrowth. There is still controversy concerning the importance of bone ingrowth or fibrous tissue ingrowth (5, 81, 106, 253). It has been suggested that currently used uncemented tibial components in total knee arthroplasty rest upon a fibrous tissue layer (5, 261) and that ingrowth of fibrous tissue could be beneficial for energy absorption by providing better distribution of stresses (161, 319, 344). In a recent study, Longo et al. (210) demonstrated a stable fibrous tissue interface around press-fit carbon composite femoral stems in dogs, which gave clinical results comparable with bony anchored HA-coated stems after a one year observation period. They concluded that bone bonding of the implant is not essential for implant success. These suggestions are supported by clinical experience where fibrous tissue anchorage is often present in clinically satisfactory prostheses (86). The observation by Ryd (261) of significant displacement of clinically stable tibia plateaus in total knee replacements confirms these in vivo observations in dogs. Furthermore, fibrous tissue interface occurs in most retrieved non-cemented metal coated hip and knee arthroplasties (44,80,81,86,107). Retrieval studies on HA-coated hip prostheses, however, have shown high percentage of bone ingrowth (29, 39, 117, 140, 239, 301).

An interesting finding in the present studies was the stronger anchorage of unstable HA implants than stable Ti implants (VII; Figure 20), despite the fact that HA-coated implants were surrounded by a thick fibrous membrane (Figure 16). One explanation might be that most of the stable Ti-implant surfaces were also surrounded by a thin layer of fibrous tissue separating the implant from surrounding bone. The distribution of bone and fibrous tissue in direct contact with the unstable HA-coated implants was not significantly different from that around stable Ti implants. As the push-out test was designed to reflect the bonding between tissues closest to the implant surface, no significant difference between stable Ti and unstable HA implants could be expected. However, additional examination of the membranes e.g. histological examination revealed presence of fibrocartilage around HA-coated implants which might partly explain the increased fibrous anchorage of HA-coated implants.

Table 9. Results from quantitative analysis of presence of fibrocartilage (percentages) in membranes around Ti-coated and HA-coated implants. Mean *SEM*

Movement	500 µm (VI)	150 µm (VII)
TI implants	2 *1.2*	5 *2.7*
HA implants	32 *21.5*	53 *11.5*

Although a strong fibrous anchorage of HA-coated implants was demonstrated, the strongest implant fixation was achieved by bone ingrowth into stable loaded HA-coated implants (Figures 18 and 20; VI, VII).

Development of a fibrocartilaginous membrane. The stability of the implant seems to be improved by presence of fibrocartilage in the membrane around HA-coated implants (Table 9) which might reduce the relative movement between implant and bone (VI, VII). This is in agreement with the interfragmentary strain theory (246) hypothesizing that presence of fibrocartilage may reduce the relative movement between bone and implant to a level where bone formation is possible. Applying the interfragmentary strain theory (246) to our bone-gap-implant situation, the fibrocartilage present at 4 weeks (VI, VII) around HA-coated implants probably reduced the strain to a level where bone could be formed, as shown in study VIII, whereas the mechanical properties of fibrous tissue around Ti implants were not able to reduce the strain to the same extent so resulting in a permanent fibrous membrane at 16 weeks.

The evolution of chondrocytes in the membrane around HA implants seems to be in agreement with in vitro studies where morphological changes from elongated to stellate shaped fibroblastic cells have been demonstrated subsequent to the phagocytosis of HA particles (134). These studies also showed increased cell proliferation and DNA synthesis in cultured fibroblastic and human bone cells when HA particles were added to the culture, and so support the increased collagen synthesis demonstrated in the membrane around HA implants (VI). The increased concentration of collagen might lead to differences in the mechanical environment and thus promote stronger mechanical properties of the membrane.

Another possible explanation for the development of fibrocartilage around HA-coated implants (VI, VII) and later conversion to bone (VIII) might be differences in hydrostatic pressure around the two implant types.

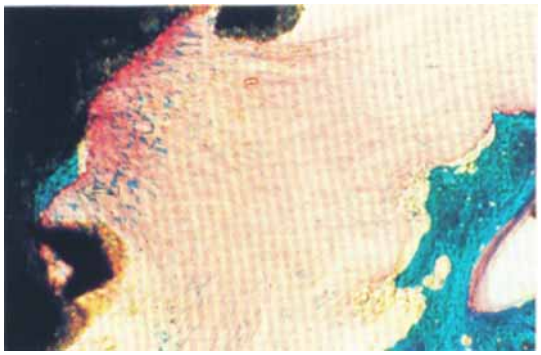


Figure 25. Photomicrograph of membrane from the unstable HA-coated implant. The collagenous fibers extend fan-shaped from the HA implant surface towards the surrounding bone. Note the precipitates of granulated material stained positive for light green located between the fibers suggesting that the membrane contains calcium-phosphate. The fibers are orientated towards a lacuna (pore) in the implant surface to terminate on the HA-coating or on an area of mineralized bone growing directly on the HA coating (arrow). Light microscopy, light green and basic fuchsin, original magnification x100.

Pauwels (244) hypothesized that tension is the specific stimulus for development of collagen fibers and compression (hydrostatic pressure) for the development of cartilaginous tissue.

Bonding capacity of collagen fibers to implant. The ligament like structures around HA-coated implants could be compared with the periodontal ligament (207) which serves as the only fixture of the tooth root to the surrounding bone. The finding that the fiber bundles often terminate either at an area of mineralized bone growing directly on the HA-coating (Figure 25) or on the HA-coating itself, might be comparable with the attachment of the periodontal ligament to the tooth cementum, i.e. a part of the periodontal ligament (Sharpey's fibers) which is embedded in the cementum and mineralized (207).

Studies on bioactive glasses have shown that collagen can be structurally integrated within the crystalized apatite (151). It is possible, therefore, that the collagen fibers are similarly embedded and bonded within the surface of the bioactive HA used in the present study. Thus, the stronger fibrous anchorage of unstable HA-coated implants compared with those of stable and unstable Ti implants could be explained by a stronger bonding capacity of collagen to HA. However, formation of a periodontal ligament around Ti implants has recently been demonstrated in the monkey mandible in regions where the implants were in close relationship to the periodontal ligament of retained root tips (57). Formation of cementum on the Ti surface was explained by presence of progenitor cells for cementum formation residing in the periodontal ligament in the retained root tips (57).

Further course of fibrous membrane. Although ingrowth of fibrous tissue into porous implants has been shown to provide adequate mechanical support for weight-bearing in dogs (210, 248) and humans (86), the long-term course of fibrous anchorage of loaded implants remains unknown. Ryd and Linder (262) recently reported on three stable fixed Marmor (cemented) knee arthroplasties revised 5–7 years after insertion for reasons other than mechanical loosening. They found fibrocartilage at the central part of the supporting tissue and suggested that presence of fibrocartilage around the prosthesis provided adequate mechanical support for a successful clinical course. However study VIII revealed that the motion induced membrane around Ti-coated implants was still present after 3 months (Figure 21B). The membrane around similar implants with HA-coating, however, was replaced by bone (Figure 21A) suggesting that in addition to the well known osteoconductive effect demonstrated in stable implants (89, 102, 255, 316), HA also seems to have the capacity to change the further course of a membrane by inducing new bone formation even during loaded conditions.

Reasons for conversion of fibrous membrane to bone (VIII) around HA-coated implants are multifactorial. Theoretically it may be explained by the presence of fibrocartilaginous tissue around HA-coated implants, as found at 4 weeks, which may prepare the gap around the implant mechanically and biologically for later conversion to bone by endochondral ossification. This explanation seems in agreement with the interfragmentary strain theory (246), which states that the initial presence of fibrous tissue in fracture healing may reduce the strain between the fracture fragments to a level where cartilage can be formed.

Also, the radiating orientation of collagen fibers (Figure 19A) and higher collagen content might contribute to a more steady mechanical milieu around HA-coated implants. The radiating fiber orientation might be similar to those described in other studies where oblique fiber orientation to the implant surface was found in membranes from a loaded Co-Cr-Mo intramedullary model (248) and porous coated Ti segmental prosthesis (148). One possible explanation for the radiating orientation of fibers is that collagen fibers might be integrated within the HA-coated surface (151). When the implant moves, load transfer will be reflected by the collagen fibers which results in radiating orientation of the fibers. In contrast, the integration between collagen fibers and the Ti surface might be weaker leaving minor load transfer in the membrane and thus giving a more random fiber orientation. It should be

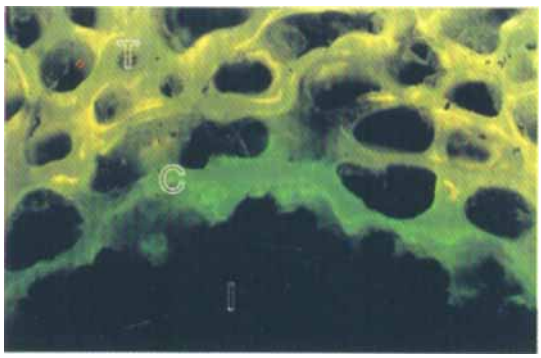


Figure 26. A continuously loaded HA-coated implant (I) showing calcein labelling (C; green) in a circular zone around the implant. Around this zone the bone is labelled with tetracycline (T; yellow). This indicates that no mineralized tissue was present in the immediate zone around the implant at the time of tetracycline labelling (8 weeks) and that mineralization in this zone occurred in the interim period between 8 and 16 weeks. Tetracycline was given at 8 weeks and calcein 3 days before termination (16 weeks). Fluorescence microscopy, original magnification x25.

emphasized, however, that a radiating orientation was also observed in membranes around some Ti-coated implants.

Other studies have demonstrated a similar presence of bone ingrowth around HA-coated implants and fibrous tissue around Ti implants (VIII) after a longer observation period. In a loaded model, Manley et al. (213) demonstrated that HA-coated intramedullary implants were anchored in bone whereas Ti-alloy implants were surrounded by fibrous tissue after 10 weeks. Another weight-bearing model with femoral hemiarthroplasty in dogs (313) showed bone apposition on HA-coated grooved macrotextured prostheses, whereas fibrous connective tissue surrounded uncoated control implants after 10 weeks. Geesink et al. (122) reported on total hip replacements with HA-coating in dogs and found similar differences after observation periods as long as 12 months. In a recent 18-month study on hemiarthroplasties in dogs, interface shear strength of HA-coated prostheses was superior to that without HA-coating which were anchored in fibrous tissue (250). Thus, HA-coating seems to be efficacious also in a more clinically relevant situation when the implant is subjected to loaded conditions during the entire observation period.

"Macrophage membrane." The further course of a persistent fibrous membrane could later lead to loosening of the prosthesis due to bone resorption caused by presence of macrophages in the membrane. According to Goldring (128) transformation to a "macrophage" membrane may be initiated by continuous movement between implant and bone. Such "macrophage" membranes around cemented prostheses have been described to contain PGE_2 and collagenase (126, 128). Presence of these substances may explain the progressive lysis of bone found around both cemented and non-cemented prostheses. In the present studies (VI, VII, VIII) macrophages were present especially around Ti implants which might suggest that these membranes would be able to produce PGE_2 and collagenase. These substances, however, were not quantified because of lack of sufficient membrane material.

Immobilization of fibrous anchored implants. Another interesting finding in the present study (VIII) was that the fibrous membrane around both HA and Ti implants were replaced by bone after subsequent immobilization. Evidently, this statement assumes that the HA-coated implants were initially surrounded by a fibrous membrane. This was evidenced by fluorescence microscopy which demonstrated the absence of mineralized tissue in a circular zone around the implants at 8 weeks whereas this zone later became mineralized in the interim period between 8 and 16 weeks (Figure 26).

Replacement of the fibrous membrane by bone is partly in agreement with Uhthoff and Garmain (337) who showed that immobilization of an unstable fracture with screws surrounded by fibrous tissue resulted in some new bone formation around the screws after 4 weeks. However, a narrow layer of fibrous tissue was still interposed between the screw and bone. They concluded that "beginning of loosening around screws can be reversed by addition of simple external immobilization". Our results (VIII) are also partly in agreement with Eschenroeder et al. (110) who presented a model with gross movement between proximal tibial trabecular bone and implant and showed that immobilization of a motion-induced fibrous membrane resulted in bone formation around and up to a porous coated Co-Cr surface. However, most of the implant surface was surrounded by fibrous tissue.

Adjuvant therapies

There is a continuing search for an enhancement of the amount of bone ingrowth leading to a better and longer lasting anchorage of the prosthetic components. Great efforts have focused particularly on local enhancement of bony ingrowth, and factors influencing this include:

- Bone grafting materials (173, 189, 196, 215, 217, 332)
- Calcium-phosphate coatings (83, 87–89, 93, 102, 122, 123, 166, 167, 313, 315, 316).
- Calcium phosphate granules (111, 173, 196, 260, 333).
- Improvement of initial mechanical stability (21, 60, 61, 100, 110, 148, 248, 249, 266, 336, 337).

Table 10. Adjuvant therapies used for enhancement of implant fixation

Type	Effect	Control implant	Implantation	Weight bearing	Observation time (weeks)	Species	Reference
Calcium-phosphate coating							
TCP/blood	–	Co-Cr-Mo alloy	press fit	–	1.5	dog	Berry et al. (37)
HA slurry	+(–)	stainless steel fiber	press fit	–	2,4,(12)	dog	Ducheyne et al. (102)
HA/TCP	+(–)	porous Ti fiber	press fit	–	(1,2),4,(6)	dog	Rivero et al. (255)
CaP Tribasic	+	Ti wire mesh	press fit	–	2,4,6	dog	Beight et al. (32)
HA coating	+	bead blasted c.p. Ti	press fit	–	5,10,32	dog	Cook et al. (83)
HA coating	–	porous c.p. Ti	press fit	–	3,6,12	dog	Cook et al. (88)
HA coating	+	bead blasted c.p. Ti	press fit	–	3,5,6,10,32	dog	Cook et al. (89)
HA coating	+	bead blasted Ti alloy	press fit	–	5,10,32	dog	Cook et al. (87)
HA coating	+	polysylphone	press fit	–	4,12	rabbit	Boone et al. (48)
HA coating	+	macrotext c.p. Ti	press fit	–	3,5,10	dog	Thomas et al. (316)
HA coating	+	smooth Ti alloy	gap (0.1 mm)	–	6,12,24,52	dog	Geesink et al. (123)
HA coating	+	grit blasted Ti alloy	press fit	–	12,25	goat	Dhert et al. (97)
HA coating	+(–)	porous Ti alloy	gap (0.2 mm)	–	2,4,6,(12)	rabbit, goat	Oonishi et al. (237)
HA coating	<+>	porous Ti alloy	press fit	–	9-10	human	Hoffmann et al. (159)
HA coating	+(–)	porous Co-Cr	press fit	–	2-4-6-(8)-12-26	dog	Cook et al. (85)
HA coating	<+(–)>	c.p. Ti screw	press fit	–	6,(52)	rabbit	Gottlander et al. (133)
HA coating	<–>	sand blasted c.p. Ti	press fit	–	12,24	human	Carlsson et al. (67)
HA coating	<+>	smooth c.p. Ti	press fit	–	12,24	human	Carlsson et al. (67)
HA coating	+	macrotex Ti alloy	press fit (gap)	–	52	dog	Poser et al. (251)
HA coating	–<+>	porous Ti alloy	press fit	–	4	dog	Søballe et al. (303)
HA coating	+	porous Ti alloy	gap (1mm)	–	4	dog	Søballe et al. (303)
HA coating	+	porous Ti alloy	gap (1mm)	–	4	dog	Søballe et al. (306)
HA coating	+	porous Ti alloy	gap (2mm)	–	6	dog	Søballe et al. (304)
HA coating	(+)	porous Ti alloy	press fit	–	4	dog	Søballe et al. (305)
HA coating	+	porous Ti alloy	gap, stable	+	4	dog	Søballe et al. (297,302)
HA coating	+	porous Ti alloy	gap, unstable	+	4	dog	Søballe et al. (302)
HA coating	+	porous Ti alloy	gap, unstable	+	4	dog	Søballe et al. (297)
HA coating	+	porous Ti alloy	gap, unstable	+	16	dog	Søballe et al. (307)
HA coating	<+>	macrotext c.p. Ti	press fit	+	5,6,10,52	dog	Thomas et al. (313)
HA coating	<–>	porous c.p. Ti	press fit	+	5,6,10,52	dog	Thomas et al. (313)
HA coating	<+>	smooth Ti alloy	press fit	+	3,6,12,24,52	dog	Geesink et al. (122)
HA coating	+	grit blast Ti alloy	press fit	+	5,10	dog	Manley et al. (213)
HA coating	+	Rough Ti alloy	press fit	+	6	dog	Klein et al. (183)
HA/TCP	<+>	Ti wire mesh	press fit, THR	+	3	dog	Jasty et al. (169)
HA coating	+	grit blasted Ti alloy	press fit	+	78	dog	Poser et al. (250)
HA coating	+	Ti mesh	press fit + screw	+	12	dog	Stulberg et al. (288)
HA coating	+	rough Ti-alloy	press fit	+	3,6,12	dog	Berger et al. (33)

+ enhancement of fixation
– no enhancement of fixation
(–) no enhancement at observation time in brackets
(+) no inhibition in osteopenic host bone
<+> superior histological response
<–> no superior histological response

- Different pharmacological agents and bone growth factors (198, 329).
- Electrical stimulation and electromagnetic fields (37, 79,270, 274, 346).
- Guided tissue regeneration (132, 345).

Bone graft materials

Incorporation of autogenous and allogenic bone graft has been studied by several investigators (8, 53, 54, 112, 124, 150, 157). Both non-weight bearing and weight bearing models have demonstrated a positive effect of autogenous and allogenic bone graft (Table 10). It is well documented that autologous bone has a higher degree of osteogenic capacity and undergoes more rapid revascularization compared to allograft (53, 125, 150). However, diminished osteogenic potential does not seem to impair the incorporation of allogenic bone graft into porous coated implants. McDonald et al. (215) found only slightly increased fixation of revised femoral components in dogs using autograft compared with fresh-frozen allograft after 12 weeks. This is in agreement with Lewis et al. (196) who found equivalent strength and bony ingrowth using autograft and fresh-frozen allograft in an unloaded dog model after four, eight and 16 weeks of implantation. However, a recent study demonstrated no effect of freeze-dried allograft in a non-weight-bearing model (179). One weight-bear-

Table 10. Continued...

Type	Effect	Control implant	Implantation	Weight bearing	Observation time (weeks)	Species	Reference
Calcium-phosphate granules							
TCP	+(–)	porous Co-Cr	gap	–	(6),24	dog	Eschenroeder et al. (111)
TCP	+(–)	porous Co-Cr	gap	–	(4),8,12	dog	Lewis et al. (196)
HA/TCP	–	fiber metal Ti	gap	+	12	dog	Russotti et al. (260)
HA/TCP	<–>	fiber metal Ti	gap	+	6,12	dog	Kang et al. (173)
HA/TCP	+	fiber metal Ti	revision hip	+	24	dog	Turner et al. (333)
Autogenous bone graft							
Autogenous	+	fiber metal Ti	gap	–	4,8	dog	Kienapfel et al. (179,180)
Autogenous	+(–)	porous Co-Cr	gap	–	(4),8,16	dog	Lewis et al. (196)
Autogenous	<–>	fiber metal Ti	gap	+	6,12	dog	Kang et al. (173)
Autogenous	+	fiber metal Ti	revision hip	+	12	dog	McDonald et al. (94)
Allogeneic bone graft							
Freeze dried	–	fiber metal Ti	gap	–	4,8	dog	Kienapfel et al. (179,180)
Fresh frozen	+	porous Ti alloy	gap	–	6	dog	Søballe et al. (304)
Fresh frozen	–	HA coating	gap	–	6	dog	Søballe et al. (304)
Fresh frozen	+	porous Co-Cr	gap	–	(4),8,12	dog	Lewis et al. (196)
Fresh frozen	+	fiber metal Ti	revision hip	+	12	dog	McDonald et al. (215)
Demineralized bone matrix							
Demineral bone matrix	+	porous Co alloy	gap	–	6	dog	McLaughlin et al. (217)
Collagen							
Bovine dermal collagen	+	porous polyethylene	press fit	–	2,4,6	rabbit	Longo et al. (211)
Electrical stimulation (μA)							
20	–	porous Co-Cr-Mo	press fit	–	1-10	dog	Berry et al. (37)
10	+(–)	porous Al_2O_3	press fit	–	(1),2,4,(8)	dog	Weinstein et al. (346)
5, 20, (50)	<+(–)>	c.p. Ti	Bone chamber	–	3	rabbit	Buch & Albrektsson (52)
50	+	porous c.p. Ti	press fit	–	1,2,3	dog	Colella et al. (79)
Electromagnetic fields							
50 kHz, 6V	<–>	porous Ti alloy	press fit, THR	+	6	dog	Schutzer et al. (270)
1.5 Hz, 1.8 G	<+(–)>	HA	press fit	–	(1),2,3,4,(6)	rabbit	Shimizu et al. (274)
1.5 Hz, 1,8 G	<–>	TCP	press fit	–	1,2,3,4,6	rabbit	Shimizu et al. (274)
Guided tissue regeneration							
Teflon membrane	<+>	c.p. Ti screw	gap	–	12	monkey	Warrer et al. (345)

+ enhancement of fixation
– no enhancement of fixation
(–) no enhancement at observation time in brackets
(+) no inhibition in osteopenic host bone
<+> superior histological response
<–> no superior histological response

ing study using autogenous bone graft has even shown inhibition of bone ingrowth compared with a negative untreated control (173). Recently, Turner et al. demonstrated advantages of a 2-stage procedure in bone grafting of non-cemented total hip replacement in dogs (334).

In study V, we reported on the gap healing effect of bone grafting around porous Ti implants and HA-coated implants and showed an enhanced fixation of grafted Ti-coated implants compared to overreamed controls. However, HA-coating used without bone graft was capable of enhancing the fixation to nearly the same degree (Figure 15). Only minor improvement was obtained when bone graft was used together with HA. As both components are known to increase bony ingrowth when used separately, this lack of measurable additive effect of adding bone graft to HA-coated implants might be explained by the presence of bone graft packed around the implant which probably eliminates the osteoconductive effect of HA.

Calcium-phosphate coatings

The effect of calcium-phosphate coating has been studied extensively in recent years and representative published shear strength values from papers comparing HA-coated and non-HA-coated implants are given in Table 10.

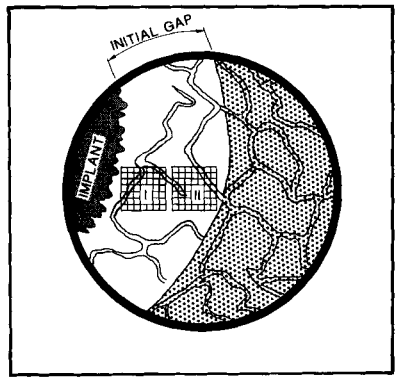


Figure 27A. The gap-healing capacity around the stable implants was quantitatively assessed in two well-defined zones from the implant surface.
Zone I: 1–6 intersections (i.e. 37–225 μm) from implant surface.
Zone II: 6–11 intersections (i.e. 225–412 μm) from implant surface.
Measurements were made on successive adjacent fields along the entire implant circumference.

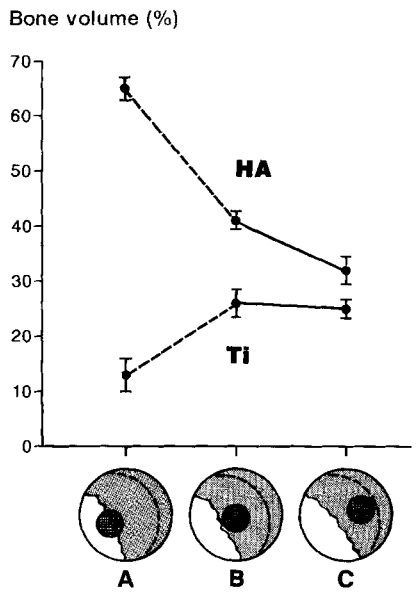


Figure 27B. Results from a quantitative evaluation of the gap-healing capacity around stable implants in two well-defined areas from the implant surface. For location of zones I and II see Figure 27a.
A. Bone apposition on implant surface.
B. New bone formation in the initial gap in zone I.
C. New bone formation in the initial gap in zone II.
Note the positive gradient of newly formed bone towards the HA-coated surface, which was not found towards the Ti-coating.

Some studies have failed to demonstrate enhanced fixation of calcium-phosphate coatings. Berry et al. (37) studied the effect of a coating consisting of a slurry of fresh blood and TCP without any demonstrable effect on implant fixation after one and five weeks' observation time. In another non-weight-bearing press-fit study (88), the authors also failed to show any effect of HA-coating compared with porous coated Ti implants, which is in agreement with a clinical study on unloaded conical implants (67).

The effect of HA-coating of course depends on the surface morphology of the control implant. An enhanced effect of HA is apparent when compared with smooth or bead blasted metal substrate (84, 89, 122).

Another series of experimental non-weight bearing studies has demonstrated a positive but transient effect of calcium-phosphate coatings (102, 255) since the stimulatory effect of HA at early time periods (4 weeks) diminished with time and the fixation approximated those implants without HA-coating at 6 and 12 weeks, respectively. The transient effect might be explained by insufficient coating techniques, as the HA powder used by Ducheyne et al. (102) was deposited by dipping the implants into a water slurry followed by drying at 80 °C, this method not being sufficient for bonding between HA and metal substrate. Rivero et al. (255) used a plasma-flame technique for application of HA powder. However, the HA powder used was transformed to TCP during the coating procedure which might explain the relatively poor effect of the coating; only 24% increased fixation was obtained at 4 weeks and no effect was obtained at the other time periods tested (1, 2, 6 weeks). One study using HA-coating in goats showed the same tendency since the enhanced fixation decreased after 6 weeks implantation to reach values obtained without HA-coating after 12 weeks (237). Gottlander and Albrektsson showed more direct bone-contact with HA-coated screws after 6 weeks, whereas there was significantly more bone-implant contact with the control c.p. Ti screws after one year (133).

A major group of non-weight-bearing and weight-bearing models with pure HA coating has demonstrated enhanced fixation or bone ingrowth for longer time periods from 3–12 weeks (48, 316), 32 weeks (83, 89), 52 weeks (123), and 78 weeks (250) after implantation compared with identical implants without HA-coating.

In studies II, IV–VII, the gap-healing capacity of bone was increased by HA-coating compared to Ti coating even at a relatively great distance (400 μm) from the HA surface (VII; Figure 27). This finding indicates that the osteoconductive effect of HA is not limited to the bone forming capacity on the surface of the implant. The positive gradient of bone occurring towards the HA surface indicates that the osteoconductive effect of HA is more pronounced close to the surface under stable conditions (VII). A pilot study

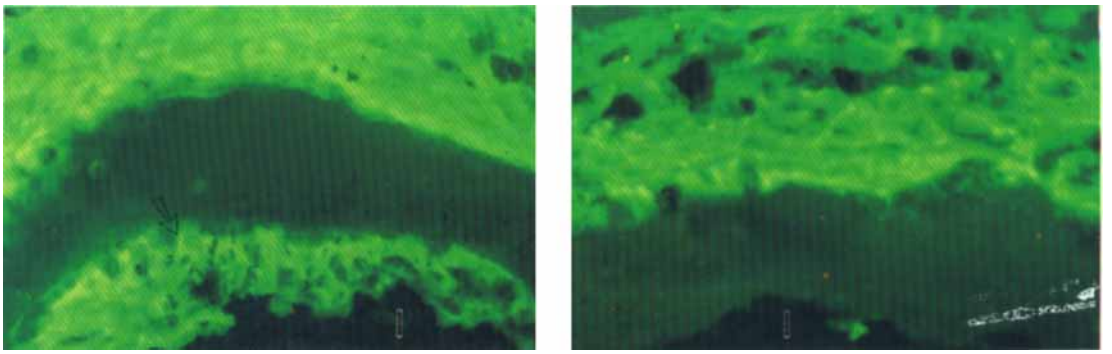


Figure 28. *Gap healing.* In order to analyse the increased speed of gap healing by HA coating, Ti and HA coated implants were inserted into the distal femur surrounded by a 2-mm gap and harvested after 2, 3, and 4 weeks. The animals were given tetracycline 10 and 3 days before termination to determine ossification fronts at different time periods. Results showed that within 3 weeks a bone plate had formed on the HA surface (left, arrow) and further filling of the gap proceeded from two ossification fronts, one from surrounding bone towards the implant, the other from the implant towards surrounding bone. This phenomenon did not take place around Ti implants (right). These findings—termed bi-directional gap healing—might explain the increased speed of gap healing using HA coating. I = implant.

demonstrated bidirectional gap healing around HA-coated implants and unidirectional gap healing around Ti implants (Figure 28). We found no comparable studies demonstrating these phenomena, but the finding may support Beight et al. (32) who suggested that calcium phosphate coating acts by providing a local source of calcium and phosphate ions essential for mineralization of the surrounding tissue. The same explanation may be used for the thinner membrane found around unstable HA implants probably caused by activation of newly formed bone at the border of the drill hole (VII). An interesting finding was the presence of bone growing directly on the surface of HA-coated implants even when subjected to micromovements. The gap-healing capacity seems to be one of the major advantages using HA-coating which is important because a major part of the prosthetic surface lacks initial contact with surrounding bone.

Several weight-bearing models have confirmed the positive effect on implant fixation using HA-coating (33, 122, 213, 250, 288, 313). Manley et al. (213) used HA-coated intramedullary implants which were demonstrated to be anchored in bone whereas Ti alloy implants were surrounded by fibrous tissue after 10 weeks. In another weight-bearing model with femoral hemiarthroplasty in dogs, Thomas et al. (313) showed bone apposition on HA-coated grooved macrotextured prostheses whereas fibrous connective tissue surrounded uncoated control implants after 10 weeks. Geesink et al. (122) reported on total hip replacements with HA-coating in dogs and found similar differences after observation periods up to 12 months. The longest observation time on HA-coated hip prosthesis known to the present author is 18 months (250). In that study Poser et al. (250) reported greater interference shear strength at all levels of HA-coated prostheses as compared with grit blasted Ti-alloy implants.

In conclusion, most experimental studies have shown a strong bonding of HA-coated implants. Variations in results may be ascribed to differences in the composition of calcium-phosphate after coating as well as different designs and testing conditions, and the surface characteristics of the control implant.

Current clinical status of HA-coated prosthetic components. So far, only a few clinical reports on HA-coated prosthetic components have been published. Geesink reported excellent results after 2 years in a recent clinical study using HA-coated components in THA (121). Freidman et al. (114) investigated the effect of HA-coating on THA components in a randomized controlled multicenter trial using press-fit non-coated Ti components of similar design as a control; Harris hip score of the HA group was significantly improved at 3 and 12 months. In a randomized study, Cook et al. (82) followed 165 patients allocated to THA with or without HA-coating and the HHS appeared superior in the HA group compared with the non-HA group after 1 year. Results from these three studies are in agreement with a recent randomized study at our hospital which showed superior clinical outcome in the HA-coated group which might be explained by the improved fixation of the femoral component as shown by the stereophotogrammetric analysis (310).

The superior fixation of HA-coated femoral components demonstrated in our study (310) is supported by Kroon and Freeman (190) who compared migration of

Ti-alloy press-fit and HA-coated femoral components using a digitizer system for measurement of prosthetic migration. These results are also in agreement with another RSA study on tibial components in total knee arthroplasty comparing 3 non-cemented groups: 1) HA-coating on a porous surface; 2) porous Ti alloy coating with screw fixation; and 3) porous Ti alloy coating without screw fixation. This study demonstrated that 3 months postoperatively, the migration was significantly less in the HA-coated group compared with both the screw fixated and the non-screw fixated porous coated groups (Nielsen et al., unpublished data). A recent RSA study on femoral components for THA showed no effect of HA-coating as compared with cemented and porous coated controls (175). In another RSA study, Carlsson et al. (66) showed that the stability of HA-coated tibial components in TKR tended to be improved as compared with non-HA-coated prostheses, but the result did not reach significance. HA-coated implants have also been used in dentistry with a success rate of 95% after 5 years (178).

Calcium-phosphate granules

The gap healing effect of TCP and HA/TCP granules has been studied extensively with variable results (Table 10). Two non-weight bearing gap studies failed to show an effect of TCP granules at early time periods (4 and 6 weeks; 111, 196) whereas a positive effect has been demonstrated after longer observation periods (8, 12, 24 weeks; 111, 196).

The use of HA/TCP granules in weight bearing models has not shown any effect on gap healing (173,260) whereas a revision hip model demonstrated enhanced bony ingrowth after a 24-week observation period using HA/TCP, but autogenous bone graft resulted in more bone ingrowth (333).

From a comparison of these results with those concerning the gap healing effect of HA-coating it can be concluded that genuine HA-coating seems to be a more reliable method for enhancing implant fixation.

Improvement of initial mechanical stability

Another way to enhance bone ingrowth is to improve the initial mechanical stability of the prosthetic component. In studies VI, VII, and VIII it was clearly demonstrated that relative motion between bone and implant inhibited bone ingrowth and resulted in the development of a fibrous membrane and a dramatic decrease in fixation as compared with stable mechanical conditions. According to these studies, probably the most significant factor for enhancing bone ingrowth and fixation is to improve the initial stability of the implant.

Different pharmacological agents and bone growth factors

Growth hormone has been documented to enhance fracture healing in rats (23–25). In our laboratory it was recently demonstrated that transforming growth factor beta (TGF-ß) enhanced new bone formation and bending strength of tibia osteotomy in rabbits (198, 199). These agents might also be capable of enhancing bone ingrowth into porous coated implants.

Recently, Trancik and Vinson showed a stimulatory effect of systemic administration of prostaglandin F_2 alpha on bone ingrowth into porous coated implants (329). Another interesting study has shown a significant increase in bone ingrowth in rabbits that were bled a volume equal to 1% of their body weight as compared with non-bled controls. This effect was ascribed an increased systemic osteogenesis (31).

Several growth factors might have a stimulatory effect on bone ingrowth and an overview of these has been made by Canalis (64).

Electrical stimulation and electromagnetic fields

The effect of direct electrical currents has been studied in the Bone Growth Chamber and is documented as increased osteogenesis (52) and to enhance the rate of bone ingrowth into porous coated implants (79, 346). Another study, however, failed to demonstrate any effect of current on bone ingrowth (Table 10; 37).

Pulsing electromagnetic fields have been shown to enhance bone ingrowth into porous HA compared with a non pulsed control group (274). However, another study on Ti fiber mesh porous- surfaced THA in dogs showed no effect on bone ingrowth using a coupled electric field (270).

Guided tissue regeneration

This new concept involving an occlusive teflon membrane has recently been shown to enhance gap healing around Ti implants in the alveolar ridge in monkeys (132, 345). Healing of radius defects in rabbits is also enhanced by a biodegradable (polyurethane) membrane (225).

Remodeling of periprosthetic bone

Bone remodeling occurs throughout life by replacement of old bone with new bone. Also bone in a porous coating and at the implant interface will later be remodelled. Hence, once bone ingrowth has occurred, maintenance of bony anchorage depends on bone remodeling

at the interface because only a fraction of the initial ingrown bone will remain after some years.

Bone remodeling is influenced by several factors such as ageing, disease and drugs. But the remodeling is also dependent on mechanical stress applied on the implant, since bone adapts to the mechanical strain to which it is subjected (Wollf's law; 353). In other words, maintenance of bone mass, structure and strength depends on the stresses applied as shown in VI and VII.

One of the problems with non-cemented THA is "stress shielding" of the proximal femur due to stress transfer through the prosthesis to the distal femur instead of stress transfer through the bone (296). Stress shielding of the proximal femur leads to proximal bone resorption and distal cortical hypertrophy, suggesting that stress is transferred distally (163, 296).

Severe bone resorption due to stress shielding might influence the long-term success of non-cemented prostheses. Several studies on the effect of different prosthetic designs (type of coating, location of coating and stem stiffness) on bone remodeling in total hip replacement have been performed (45, 46, 290, 294–296, 300, 330). From these studies it can be concluded that stem stiffness is an important factor for bone remodeling since flexible stems result in less bone resorption (295).

Conclusion

1. A gap between bone and Ti-coated implants resulted in significantly weakened fixation compared with press-fit insertion (I). In contrast, HA-coating enhanced bone ingrowth in the presence of an initial gap between bone and implant (I,IV,V,VI,VII), even in the presence of osteopenic host bone (IV).
2. In press-fit, HA-coating also enhanced bone ingrowth (I) even when surrounded by osteopenic host bone (III).
3. Carragheenin-induced arthritis of the knee resulted in substantial bone loss (osteopenia) of the femoral condyles (II).
4. In osteopenic bone, a weakened bone-implant fixation was observed using Ti-coated implants whereas HA-coated implants were not affected by the osteopenic condition in the bone bed (III). However, the fixation of Ti-coated implants was superior to that of HA-coated implants in normal bone (III).
5. Allogenic cancellous bone graft enhanced fixation of Ti implants significantly. However, HA- coating alone (without bone graft) offered almost the same improvement in anchorage by enhancing bone repair in 2-mm defects (V).
6. Arthritic bone changes did not influence incorporation of allogenic bone graft (V).
7. Micromovements between bone and implant inhibited bony ingrowth and resulted in development of a fibrous membrane (VI, VII). This fibrous membrane consisted of fibrocartilage (VI, VII) and had a higher content of collagen (VI) when the implant was coated with HA.
8. A stronger fibrous anchorage was obtained with unstable HA-coated implants compared with both unstable (VI) and stable (VII) Ti-coated implants.
9. The best anchorage and the greatest amount of bone ingrowth was obtained by the loaded mechanically stable implant coated with HA (VI, VII).
10. HA-coating seemed to have the capacity to replace a motion-induced fibrous membrane by bone even when subjected to continuous load (VIII). In contrast, a fibrous membrane remained around Ti-coated implants subjected to similar loading conditions (VIII).
11. The consequence of immobilization of motion-induced fibrous anchored implants was a replacement of the membrane by bone, irrespective of type of coating. A greater amount of bone ingrowth was obtained with immobilized HA-coated implants compared with immobilized Ti implants (VIII).

Suggestions for future research

The surveyed studies have mainly described the short-term effect of HA-coating on the periprosthetic tissue. After completing these studies, however, many questions arose especially on the long-term behavior of HA-coating.

The question about resorption of HA has still not been elucidated, and further studies with special emphasis on resorptive characteristics would improve our understanding of the long-term behavior of HA-coatings.

Particulate HA has been demonstrated to inhibit bone cell proliferation and increase cytokine production in vitro (76, 193). These adverse biologic responses of particulate HA should be studied in vivo models.

Polyethylene wear debris has been implicated in the etiology of loosening of prosthetic components and studies on a possible sealing effect of HA-coating to prevent polyethylene particles from migrating along the bone-implant interface would be of great interest.

There is still considerable controversy concerning the importance of ingrowth of bone or fibrous tissue. The long-term outcome of fibrous anchored prostheses compared with bony anchored prostheses would be of significant interest for future studies.

Another long-term objective for future research would be to improve the success rate for revision joint replacements. The controlled micromotion device developed for the present thesis might be a tool for identification of the conditions and mechanisms of failure that distinguish revision from primary joint replacements.

To further enhance bone ingrowth into porous coated implants, HA could be used as a carrier for growth factors such as TGF-ß which might be applicable for future studies.

Since the initial mechanical stability of prosthetic components seems to be one of the dominant variables in obtaining bone ingrowth, research in the future should concentrate on improving the primary fixation mechanisms. Also the timing and degree of loading during stabilization of an implant in humans need to be more fully understood.

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