Fixation of Spinal Implants

Clinical and Experimental Studies on the Effects of Hydroxyapatite Coating

BY

BENGT SANDÉN
Loosening of implants is a frequent complication in orthopaedic surgery. The aim of this thesis was to evaluate hydroxyapatite coating of pedicle screws with mechanical and histological methods and to correlate the results with the radiological findings.

Hydroxyapatite (HA) coating of pedicle screws was investigated in experimental studies in sheep. Nine sheep were operated on with destabilising laminectomies at L2-L3 and L4-L5 and stabilised with pedicle screw instrumentations, where HA coated and uncoated screws were used in a randomised fashion. After both 6 and 12 weeks of implantation, the HA coated screws demonstrated a higher bone-to-implant contact and a higher amount of bone in the area close to the screw. The pull-out resistance, stiffness and total energy to failure was higher for the HA coated screws after 12 weeks of implantation.

HA coating of pedicle screws was examined in two clinical studies. In the first series, the patients were stabilised with pedicle screw instrumentations, where HA coated screws were used in either the upper or lower instrumented level in a randomised fashion. After 10-22 months of implantation, the extraction torque was markedly higher for the HA coated screws. In the second series, instrumentations with uncoated, partly HA coated or fully HA coated screws were used. After 11-16 months implantation, the extraction torques were recorded. There were significant differences between all three groups, with the lowest extraction torques for the uncoated screws and the highest torques for the fully HA coated screws. The frequency of radiolucent zones surrounding the screws was higher for the uncoated screws than for the HA coated screws.

Radiographs from both experimental and clinical studies were examined. Screws demonstrating radiolucent zones were compared to screws without zones with respect to pull-out resistance, extraction torque, bone-to-implant contact and amount of bone surrounding the screws. All these variables demonstrated higher values for the screws without radiolucent zones. The frequency of radiolucent zones surrounding uncoated screws in the clinical study was 53%.

Conclusions: Radiolucent zones are good predictors of screw loosening. The frequency of radiolucent zones is higher than previously described. Hydroxyapatite coating improves the purchase of pedicle screws and reduces the frequency of screw loosening.

Key words: Hydroxyapatite, pedicle screw, histomorphometry, fixation, radiolucent zones, screw loosening.

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To Ingrid and Lisa
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INTRODUCTION

Spinal instrumentation

The use of screws for internal fixation in spinal surgery was first described by King, who used oblique transfacet screws for lumbosacral fusion [46]. In 1970, the use of pedicle screws was described by Roy-Camille and co-workers [74]. The use of pedicle instrumentation has increased gradually, and pedicle screws now are used as routine in spinal surgery. The significance of instrumentation with pedicle screws on the healing rate of spinal fusions has been debated, as in some studies no differences could be found between the healing rates of instrumented and non-instrumented fusions [4, 91]. However, there has been significant increases in fusion healing for instrumented fusions in other clinical studies [28, 97, 98], as well as in animal models [44]. The Cochrane review stated that there is strong evidence that instrumented fusion may produce a higher fusion rate than non-instrumented fusion [31]. Instrumentation with pedicle screws also is used for other applications than spinal fusion, such as fractures and tumours of the spine. For these applications, even more than for surgery for degenerative disorders, the success of the operative procedure is depending on a good fixation of the implants to the spine.

Fixation and loosening

The aim of spinal instrumentation is to maintain stability until fusion or fracture healing has occurred. When pedicle screws are used, the stability of the system is depending on the ability of the screws to maintain their purchase in the pedicle and the vertebral body. Loosening of the screws results in a loss of stability that might lead to non-union or loss of reduction. Many reports have focused on the complications of pedicle screw fixation, including the frequency of screw loosening. McAfee et al reported on 526 pedicle screws, out of which 3% were broken, but none were loose [56]. In a survey analysis by Esses et al of 617 cases treated by members of the American Back Society, the rate of screw loosening
was 0.81%, and screw breakage 2.9% [25]. The study by Esses et al included an extensive literature review, with a frequency of screw loosening varying from 0.6% to 11%. In a historical cohort study by Yuan et al, screw loosening was observed in 2.8% and screw breakage in 2.6% of 2153 patients treated for degenerative spondylolisthesis [97]. These studies with low rates of loosening and breakage of the screws do not comment on radiological methods or the criteria for screw loosening. In three studies with thorough descriptions of the radiological examinations and including in two of them strict criteria for screw loosening, the loosening rates were 21%, 18% and 27%, respectively [64, 71, 85]. The frequencies of screw breakage were 6%, 21% and 16%, respectively. In all these studies with very varying rates of screw loosening, stainless steel screws were used, with very few exceptions. In most studies screws of different designs and from different vendors were used. Therefore, it seems unlikely that the varying results could be explained by differences in materials and screw designs. The varying frequencies of radiological screw loosening in these studies could rather be explained by the differences in study design, with different definitions of screw loosening, and great variation in the follow-up of the patients. It seems likely that the frequency of loosening has been underestimated in several of these studies.

The fixation of pedicle screws depends on several factors. The major factors are the quality of the bone and the design and size of the screws [9, 50, 86]. The mechanism of failure of pedicle screw systems has been controversial. According to Spivak, the main failure mode is by pull-out, while unscrewing is not a failure mode seen clinically [87]. The ability to resist pull-out is dependent on the outer thread diameter of the screw, the shear strength of the bone at the outer thread margin, and to a lesser degree on the thread pitch and angle [2, 27]. On the other hand, some authors claim that axial pull-out represents bone strength and does not reflect screw failure in the clinical situation [8]. According to Christensen, the rotational stability of the screw is essential to maintain the stability of the whole construction, and the rotational stability is best reflected by the extraction torque of the screw. The insertion torque is generated primarily by the shearing force and friction in the bone-screw interface [65], and is dependent
on the size of the screw and the quality of the bone in the interface. Some authors
describe the mechanism of loosening of pedicle screws as a cyclic toggling under
caudocephalad loads [53, 65, 100]. Also with this proposed mechanism, the
bone quality and the size of the screw are important factors. The diameter of the
screw is limited by the size of the pedicle, and could not be further increased.
Thus, the most effective way to improve the purchase of pedicle screws is to
improve the bone quality and increase the amount of bone surrounding the
screws.

**Bone and CaP materials**

Bone is composed of an organic collagenous tissue, mainly type I collagen,
and an inorganic mineral phase, together forming a composite structure. The
composition of the mineral phase varies between different parts of the bone and
over time, but the main constituent of bone mineral is hydroxyapatite
$[Ca_{10}(PO_4)_{6}(OH)_2]$ [89]. Hydroxyapatite (HA) is a calcium phosphate ceramic.
Ceramics are solid compounds of metals with non-metals. When ceramic
compounds are formed, generally a large amount of energy is released. These
compounds are in a low energy state, meaning that further spontaneous reactions
are unlikely to occur. Due to this, ceramics are the most chemically and
biologically inert of all materials [11]. HA and tricalcium phosphate are not as
inert as most other ceramics, and tend to be less strong and more chemically
reactive [11]. Calcium phosphate ceramics are highly biocompatible, and due to
the chemical similarity to the natural bone mineral, they are capable of forming a
direct biochemical bond with bone [89]. The calcium phosphates of biological
interest are calcium salts of orthophosphoric acid [41]. There are six principal
calcium orthophosphates; dicalcium phosphate dihydrate, dicalcium phosphate
anhydrous, octacalcium phosphate, $\beta$-tricalcium phosphate, hydroxyapatite and
tetracalcium phosphate monoxyde. Out of these six compounds, the first three
are too soluble to be used for biomaterials [41]. Many ionic substitutions may
occur in HA, for example the hydroxyle group may be replaced by fluoride, and
the compound is then named fluorapatite. $\beta$-tricalcium phosphate and HA are the
most commonly investigated calcium phosphates. The term tricalcium phosphate is used for any pure calcium phosphate with a Ca/P atomic ratio equal to 1.50 [41]. The term does not imply either a composition or a structure. Tricalcium phosphate is a naturally occurring component of mineralised tissues. It is resorbed to a greater extent and more rapidly than HA [42]. In contrast to tricalcium phosphate, synthetic HA is not readily bioresorbable in appropriate forms, and it is therefore suitable for long-term clinical applications [89]. Due to these properties, HA has been more thoroughly investigated than other calcium phosphate materials. HA materials have been used in particulate forms, as pastes mixed with collagen or other materials, and also in dense solid or composite forms. The Ca/P atomic ratio of pure HA is 1.67. Several characteristics differ between bone apatite and the apatite of HA coatings. The HA in bone is more inhomogeneous with lack of crystal and chemical perfection, and it is also more reactive than HA coatings due to the large surface area of trabecular bone [67].

Like other ceramics, HA is a brittle material with low tensile strength, while the compressive strength is high. In order to combine the mechanical properties of metals with the biocompatibility of ceramics, coatings of calcium phosphate ceramics have been developed. The coated implants have the advantages of the metallic material in terms of mechanical strength and other physical properties, along with the biological benefits of the coating [89]. Many different techniques have been used to apply the coating to the substrate metals, like electrophoresis, dipping and mechanical methods. The most commonly used technique is plasma spraying, introduced in the early 1980s [32]. An electric arc is struck between the cathode and the anode, while a stream of gases passes through the arc. This results in a ionised gas with a temperature up to 30,000°C. The temperature increase gives a large expansion, and a velocity of the plasma stream approaching the speed of sound. The coating powder is introduced into the plasma stream, usually in a carrier gas, and then melted and propelled onto the substrate with a speed of at least 200m/s. Solidification then occurs very rapidly, and the coating is formed. Because of the high plasma temperature, the coating material may be altered during the process, resulting in a chemically or structurally different material as the final product. According to some authors, all
plasma-sprayed commercially available HA coats have undergone phase changes. [21] The properties of the HA coating also is affected by the composition and purity of the starting powder material. Due to these factors, the HA coatings from different manufacturers may vary significantly in structure, purity, composition and crystallinity. HA coatings from different manufacturers demonstrate varying histological and mechanical characteristics [14]. A variability of the coatings from a manufacturer may also be expected, and it has been recommended that surgeons using HA coated prosthetic devices request a quality report for each batch delivered before inserting the prosthesis [80]. The optimal properties of HA coatings, like for example thickness, have been debated. The mechanical properties of the coating are improved with decreasing thickness of the coat [92]. On the other hand a thicker coat is more stable as it is less sensitive to dissolution, and a compromise between these factors must be done [47]. For other properties, such as purity, chemical composition, Ca/P ratio, trace element content, crystallinity, density, porosity, solubility and mechanical properties, several standards have been proposed and published [3, 20, 26].

**The metal substrate**

For most HA coated implants bearing significant loads, titanium alloys, cobalt-chrome alloys or stainless steel are used. The mechanical properties differ
between these different materials; for example the elastic modulus of cobalt-chrome is higher than the elastic modulus of titanium alloy (Ti-6Al-4V). The biocompatibility of both titanium alloy implants and cobalt-chrome implants are favourable [67]. In vitro, osteoblasts have been demonstrated to grow faster on titanium alloy (Ti-6Al-4V) than on cobalt-chrome alloy or stainless steel [72], and the biocompatibility of titanium has been described as superior to that of cobalt-chrome and stainless steel [40]. However, in most studies of the biocompatibility of titanium, commercially pure (c.p.) titanium has been used. C.p. titanium is used as routine for oral implants, and show clearly better results in the long-term perspective than HA coated implants [1]. Due to the limited strength of c.p. titanium, it is not used for pedicle screw instrumentations. Instead titanium alloys are used, mostly Ti-6Al-4V. There is no data backing up the concept that titanium alloy is as well accepted in bone, as is c.p. titanium [43]. HA coating adheres stronger to a titanium than to a cobalt-chrome substrate [22]. However, HA coatings of titanium and cobalt-chrome implants have been examined in an experimental study. Both mechanically and histologically, the HA coated cobalt-chrome implants performed in a similar manner to the HA coated titanium implants [29].

Experimental studies

Numerous studies of implants in unloaded animal models have indicated a more rapid bone response to HA coated implants when compared to uncoated implants [34, 35, 39, 66, 84, 90]. A review of these and other short-term studies implies a maximum for the bone-to-implant attachment after 6 to 12 weeks for HA coated implants. The long-term effects of HA coated implants in unloaded experimental studies have been uncertain. At one year after insertion there seems to be no evidence of any difference in fixation strength between HA coated implants and uncoated controls. The percentages of bone-to-implant contact have varied between different studies, and higher, similar and lower contact percentages have been reported [1].

HA coating of stainless steel external fixation pins has been investigated in loaded animal models. Using a sheep model, both the extraction torque and the
bone-to-implant contact was significantly higher for the HA coated pins when compared to uncoated controls after 6 weeks [6]. In another study using a similar model, the extraction torque was significantly higher for the HA coated fixation pins after both 4 and 12 months of implantation. Both the percentage of bone-pin contact and of bone present between the threads was higher in the HA coated pins when compared to the uncoated controls [61]. The effects of HA coating of external fixation pins have also been compared to the effects of coating with plasma-sprayed titanium. After six weeks of implantation, the extraction torques were significantly higher for both the HA coated and the titanium coated pins when compared to the uncoated stainless steel pins, while the extraction torques for the HA coated pins were significantly higher than the torques for the titanium coated pins. There was no difference regarding the percentage of bone-pin contact between the HA coated and titanium coated pins [62]. In a study on dogs, HA coated AO/ASIF screws were used for fixation of fractures, and compared to uncoated stainless steel screws. After 4 and 8 weeks of implantation, the removal torques of HA coated screws were significantly higher than the torques of the uncoated screws [15].

HA coating of unloaded spinal implants has been investigated in two experimental studies. Augmentation of fixation of pedicle screws and iliac rods with plasma-sprayed coating of HA has been examined in dogs. The HA coated screws were somewhat less resistant to pull-out than the standard screws 6 weeks after implantation, even though the difference was not significant. Microscopy revealed a section of shear failure through the HA coating at each thread, lowering the shear strength at the outer margin of the thread. Coating of the iliac rods gave a significant increase of pull-out strength at 6 weeks, whereas the uncoated rods showed a significant decrease in holding power at 6 weeks, when compared to the pull-out strength directly after insertion [87]. In a study using an unloaded sheep model, HA coated titanium pedicle screws were compared to stainless steel screws and uncoated titanium (Ti-6Al-4V) screws. After 4 months of implantation, the extraction torque and the percentage of bone-to-implant contact were higher for the HA coated screws than for the stainless and uncoated screws, respectively [73].
In a model with loaded spinal instrumentations in mini-pigs, titanium (Ti-6Al-4V) pedicle screws have been compared to stainless steel screws [8], but there are no experimental studies of HA coating of loaded spinal instrumentations.

**Clinical studies**

In total hip arthroplasty, applications of HA coatings are well-documented with promising clinical and radiological results [88]. In two recent studies, HA coated femoral stems have demonstrated good clinical results [38, 58].

In external fixation, HA coating has been studied in order to improve the fixation of the fixation pins. In patients undergoing hemicallotasis for osteoarthritis of the knee, HA coating of fixation pins resulted in significantly higher extraction torques and a reduced frequency of loose pins, when compared to uncoated controls [55]. In patients with tibial fractures, the HA coated pins demonstrated significantly higher extraction torques when compared to stainless steel fixation pins. None of the 7 patients receiving HA coated pins had pin tract infection, while half of the patients receiving uncoated pins had infections [59]. In another study of external fixation, HA coated external fixation pins had a lower rate of pin tract infections, and there were no differences in fixation strength between infected and uninfected HA coated pins [60].

The preliminary experience with the use of HA coated pedicle screws in 27 patients has been reported. The clinical results of the patients were described, as well as the frequency of healed fusions. However, the authors did not comment on the purchase of the screws, or the frequency of radiological signs of screw loosening [52].
AIMS OF THE STUDY

The primary aim of this study was to evaluate hydroxyapatite coating of pedicle screws, in order to reduce the problems with screw loosening in spinal instrumentation. A secondary aim was to correlate the radiological findings in spinal instrumentation with the purchase of the screws and the histological picture, in order to improve the diagnosis of screw loosening.

The specific aims of the different studies were as follows:

- To evaluate the effects of HA coating of pedicle screws when used in only one of two instrumented levels (paper I).
- To study biomechanically the effects of HA coating of pedicle screws in a loaded animal model (paper II).
- To investigate the effects of HA coating of pedicle screws on the bone surrounding the screws and the bone-to-screw interface (paper III).
- To evaluate the effects of HA coating when used in all four screws in an instrumentation, and also to study the effects of coating of a part of the screw only (paper IV).
- To correlate the radiological findings in spinal instrumentations with the mechanical and histological findings (paper V).
MATERIALS AND METHODS

Implants

In the clinical studies (papers I, IV), the Posterior Fixator System (Nordopedic, Gothenburg, Sweden) with stainless steel (SAF 2507) screws was used for the instrumentations. In the first study (paper I), the diameters of the screws were 5 or 6 mm, and the lengths 55 - 70 mm. All HA coated screws in that study were fully HA coated. In the second study (paper IV), only 6 mm screws with lengths 55–75 mm were used. Both fully and partly HA coated screws were used (fig 2).

Figure 2. 6 x 70 mm pedicle screws: uncoated (upper), partly HA coated and fully HA coated.
In the experimental studies (papers II, III), the Posterior Fixator Mini System (Nordopedic, Gothenburg, Sweden) was used. The screws were made of stainless steel (SAF 2507). The total length of all screws was 40 mm, and the diameter 4 mm. The threaded portion was 15 mm and the HA coating also covered 8 mm of the unthreaded portion, so that 23 mm of the screws were HA coated. The uncoated part of the screw was used for the connection of the instrumentation, and not implanted in bone (fig 3).

![HA coated and uncoated screws](image)

**Figure 3:** HA coated (upper) and uncoated screws, used in the experimental studies.

The HA coating was applied with plasma-spraying technique by CAM Implants B.V., Leiden, Netherlands. The coating thickness was, as controlled by the manufacturer, approximately 45 µm, the density >95%, and the crystallinity 55% for all three batches used. One screw from the batch used in paper I was embedded and sectioned, and the thickness of the coating was measured with histomorphometry. The coating thickness of that screw was 40 µm, on average. The implants were delivered in sterile packages after sterilisation by gamma-irradiation. One new HA-coated implant from the batch used in paper I was analysed for material composition in a JEOL JSM 5800 scanning electron
microscope equipped with a Link ISIS energy dispersive X-ray system (SP Swedish National Testing and Research Institute, Borås, Sweden). The uncoated implant part that was semi-quantitatively analysed demonstrated a composition of 63% Fe, 26% Cr, 7% Ni and 4% Mo. The semi-quantitative analysis of the coating revealed 43 weight% oxygen, 39% calcium, 17% phosphorus and about 0.5% magnesium.

Figure 4. Scanning electron micrographs of the HA coat of a 6 x 70 mm pedicle screw.

**Experimental studies**

Thirteen adult female sheep, all approximately 2½ years old and of similar weight (59-63 kilograms) were used. Nine sheep were operated on, while four additional sheep, killed for other reasons, served as 0-week controls for the biomechanical variables. All surgical procedures were performed using general anaesthesia, which was induced with thiopental sodium and maintained with nitrous oxide and 2% isoflurane under assisted ventilation. Prophylactic antibiotic therapy (bensylpenicillinprocaine) was administered intravenously during surgery. The posterior elements and transverse processes were exposed through a midline incision. Destabilisation was performed with laminectomies and excision of the facet joints between the second and third and the fourth and fifth lumbar vertebrae, respectively. All the posterior elements were removed,
leaving only the intervertebral discs connecting the segments. No attempt was made to achieve fusion between the vertebrae; instead all bone fragments from the destabilisations were carefully removed in order not to get fusion of any segments. The cortical bone was penetrated with the use of an awl, and the pedicle holes were prepared with a probe and then tapped with a 4-mm tap corresponding to the entire length of the screw. Transpedicular screws were applied bilaterally from the second to the fifth lumbar vertebrae.

Two instrumentations with four pedicle screws in each were mounted, with one instrumentation bridging the L2-L3 level, and one bridging L4-L5. In a randomised fashion HA-coated screws or uncoated screws were used in either the upper or the lower instrumentation. The screw positions were documented with lateral and antero-posterior radiographs. The subcutaneous tissues and the skin were closed in separate layers. The same two surgeons performed all the surgical procedures. The study was approved by the Uppsala regional ethics committee for animal experiments.

Two animals were euthanised early due to deep wound infection in one and postoperative neurological disturbance in the other. The remaining seven animals completed the study period. Three animals were killed at 6 weeks and four animals at 12 weeks. The spines were removed en bloc, and the soft tissues removed from the fresh specimens. As the connecting rods were disassembled, it

Figure 5. Radiograph of preparation of L2, demonstrating the insertion of pedicle screws in the experimental study.
was noted if any screw was apparently loose. The specimens were divided with an oscillating saw through the levels of the discs and facet joints, leaving separate vertebrae with two pedicle screws in each.

![Image](image_url)

**Figure 6.** Preparation of lumbar spine from a sheep sacrificed after two weeks due to wound infection. Destabilisation and fixation with pedicle screw instrumentations L2-L3 (left) and L4-L5 (right).

Each animal had four HA coated and four uncoated screws, and thus served as its own control. Following a schedule, two HA coated and two uncoated screws from each animal were used for the biomechanical study (paper II), making sure that all vertebral levels were represented in each group. In a similar manner two HA coated and two uncoated screws from each animal were used for histology and histomorphometry (paper III). In the four animals serving as 0-week controls for the biomechanical evaluation, two HA coated and two uncoated screws were applied in each animal. Thus, 44 screws were used for biomechanical studies (paper II), and 28 screws for histology and histomorphometry (paper III).
Table 1. Number of screws at different times of follow-up in the biomechanical study (paper II).

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<th>0 weeks</th>
<th>6 weeks</th>
<th>12 weeks</th>
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<tr>
<td>No. of screws</td>
<td>16</td>
<td>12</td>
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Table 2. Number of screws at different times of follow-up in the histological study (paper III).

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<th>0 weeks</th>
<th>6 weeks</th>
<th>12 weeks</th>
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<tr>
<td>No. of screws</td>
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<td>12</td>
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For the biomechanical testing, a servo-hydraulic material testing machine was used (Mini Bionix 858, MTS Corp, Minneapolis, MN, USA). The specimens were placed in the testing machine vertically aligned along the screw axis. The free end of the screw was attached by a hydraulic grip to the testing machine. A purpose built fixture that ensured stable fixation of the vertebrae was attached to the load cell. Axial pull-out was applied at a rate of 0.5 mm/s while load and displacement was recorded at a sampling rate of 50 Hz (Teststar II data acquisition with software Testware SX version 3.1, MTS Corp, Minneapolis, MN, USA). Based on the data collected the maximum pull out load (N), stiffness (N/mm), and energy (Nmm) to failure was calculated for each screw. Two stiffness values were determined with “Stiffness A” defined by the tangent of the slope for the early linear portion of the load-displacement curve while “Stiffness B” was defined as the quotient between maximum load and the displacement produced by that load. The area under the load-displacement curve to the maximum load defined energy to failure.

For the histological and histomorphometric evaluation, the specimens were divided with a saw, leaving less than 10 mm of the vertebral bone surrounding each of the screws. The implants with surrounding bone were then immersed in
4% neutral buffered formaldehyde followed by dehydration in graded series of ethanol, diluted resins and finally embedding in pure resin (Technovit VLC 7200, Kulzer, Germany). The polymerised samples were cut in the long axis of the screws using the Exakt equipment (Exakt Apparatebau, Norderstedt, Germany). The specimens were then ground to a final thickness of approximately 10μm and stained with toluidine blue [19].

The histological analysis was carried out using a Leitz Aristoplan (Wetzlar, Germany) light microscope equipped with a Leitz Microvid unit connected to a PC and a mouse enabling the observer to perform histomorphometric measurements directly in the eye-piece of the microscope. An objective of 10 x, i.e. a magnification of 100 x and a zoom of up to 2.5 x were used for the quantitative histomorphometry. The aim was to study all twelve complete screw threads with respect to the percentage of bone-to-implant contact and the relative amount of bone in two different areas. The first bone area was defined as the area between the screw and a line connecting the top of the threads (inner thread area), while the second area was immediately lateral to the first area and of the same size, reflecting a mirror image of that area (mirror area).

**Figure 7. Inner thread area and mirror area**

Both conventional light and polarised light was used in the histomorphometric evaluation. By using polarised light it became possible to differentiate between bone-resembling tissue and bone in doubtful areas. The areas that did not polarise were not regarded as bone in the histomorphometric calculations.
Clinical studies

Both clinical studies (papers I, IV) were prospective studies where HA coated pedicle screws were compared to uncoated controls. Informed consent was obtained from all patients before they were included in the studies. The studies were approved by the Medical Ethics Committee. In both studies, randomisation occurred by using closed envelope technique immediately before surgery. Standard anatomical landmarks were used for identification of the pedicles, and fluoroscopy was used for confirmation of the positions of the screws. A pedicle probe was used for the preparation, and the holes were tapped with a tap of the same diameter as the screw and corresponding to the entire insertion depth of the screw.

Insertion and extraction torques were recorded using a torque gauge manometer with a range of 5-600 Ncm (Eduard Wille GmbH & Co, Wuppertal, Germany). The recordings of insertion torque were taken as the torque just when the entire threaded portion of the screw had been implanted into bone. The maximum extraction torques were recorded. All the instrumentations were four-screw constructions, and all fusions were one-level or two-level fusions.

All extraction procedures and all recordings of extraction torque were performed by the same surgeon. During surgery, fusion healing was evaluated by manipulating the fused area with pliers. In doubtful cases the fusion mass was explored.

Paper I: Seven patients were operated on. In each patient, two HA coated pedicle screws and two uncoated screws were used. The HA coated screws were applied in either the upper or the lower of the instrumented levels in a randomised fashion. In four patients, the screws were removed after 10, 14, 15 and 22 months, respectively. Out of these four patients, three were female. Their mean age was 33 years and the indications for surgery were postdiscectomy syndrome in two cases, spinal stenosis and fracture of Th 12 in one case each.
Three different surgeons performed the four surgical procedures. All pedicle screws were judged to be correctly placed on the basis of the postoperative radiographs. The fusions were healed by the time of extraction in all four patients.

Two screws that had been removed with bone still attached made it possible to analyse the bone-implant interface histologically. The methods described for the experimental studies were used for the preparation.

**Paper IV**: 23 consecutive patients planned to undergo instrumented one- or two-level lumbar or lumbosacral fusions for degenerative disorders were included in the study. The indications for surgery were spinal stenosis in 10 cases, spondylolisthesis in 9 cases and chronic disabling low back pain in 4 cases. The mean age was 56 ±12 years, 14 women and 9 men. The vertebrae instrumented were L3 (12 screws), L4 (24), L5 (30) and S1 (26 screws). The patients were assigned to one of three treatment groups: Uncoated pedicle screws, screws where the distal 50% of the threads was coated with HA (partly HA coated group), and screws where the entire implanted portion of the screw was coated (fully HA coated group). Partial or total laminectomy was performed in all patients but two, and both these patients were in the partly HA coated group. All implants were planned to be extracted after one year. In 21 of the 23 cases, the instrumentations were performed by the same surgeon, and in these 21 cases, the insertion torque was recorded.

Radiographs were taken preoperatively, postoperatively, 3 and 6 months after surgery and before extraction of the instruments.

After 11-16 months (average 12.4), the instruments were removed in 21 of the 23 patients. One patient did not undergo extraction due to other diseases, and one patient was lost to follow-up. The two patients that did not have their instruments extracted were not the same two individuals that did not have any insertion torque measurements, and thus data from both insertion and extraction were available for 19 patients. Due to technical problems, no readings of extraction torque could be taken in four screws in three different patients in the partly HA coated group and in one screw in the fully HA coated group.
Radiology

In the experimental study, the radiological examination was performed following removal of all soft tissues from the lumbar spines immediately after sacrifice. All screws were radiographed using four different views including two lateral and two anteroposterior views, both with cranial and caudal angulations according to a study protocol. Conventional x-ray film-screen combinations were used. The radiographs were evaluated with respect to screw positions and radiolucent zones by a radiologist without knowledge of the mechanical or histological findings. If a radiolucent zone was noted, the maximal width of the zone was recorded, disregarding the length of the lucency.

In the second clinical study (paper IV), lateral and anteroposterior views were taken. Apart from the preoperative x-rays, all examinations also included two lateral views with cranial and caudal angulations and two anteroposterior oblique views according to a study protocol, in order to evaluate screw positions and radiolucent zones around the screws. Conventional x-ray film-screen combinations were used. The radiographs were evaluated by a radiologist without knowledge of the extraction torque. A wide radiolucent zone surrounding the screws was defined as lucency >1 mm, disregarding the length of the lucency. A thin radiolucent zone was defined as lucency with a width of 1 mm or less. The HA coat is not visible on the radiographs and does not affect the evaluation of radiolucencies. This also applies to the hydroxyapatite coated screws used in the experimental study.
**Statistics**

The statistical calculations were performed using the Mann-Whitney U-test (I-V), the Wilcoxon signed-rank test (II-III) and Fisher’s exact test (I-II). The Kruskal-Wallis test and the Chi-square test for three independent samples were used in the second clinical study (IV).

In papers II and III, implant pairs with HA coated and uncoated screws were studied, using the Wilcoxon signed-rank test. As two implant pairs were studied from each animal, a three-way analysis of variance with Bonferroni corrections also was performed.
RESULTS

**Paper I**

The mean insertion torque was 107±37 Ncm for the HA-coated screws and 76±29 Ncm for the standard screws ($P<0.05$).

In 3/4 patients the maximum torque for the HA-coated screws exceeded the upper range (600 Ncm) for the torque manometer, while the standard screws were completely loose, i.e. the screws rotated when the torque gauge manometer was applied. No reading could therefore be taken. For the statistical evaluation, the values for extraction torque for these screws were set to 600 Ncm and 5 Ncm, respectively. The difference in extraction torque between the groups was significant ($P<0.01$).

The HA-coated screws in three patients could not be removed with the conventional screwdriver. In one patient the screws had to be removed together with a thin zone of the surrounding bone by using a cannulated drill. No complications were noted after the removal of the screws.

The histologic examination of the two screws extracted with surrounding bone demonstrated an irregular HA coating intermingled with bone-stained acellular tissue, reaching out at some distance from the coating layer. The acellular tissue did not polarise. There was a clear demarcation between this tissue and the normally polarising bone structure. The implants were surrounded by a more lamellar bone tissue in the outer portions, whereas in the vicinity of the implants the tissue was more woven.

The thickness of the HA coatings was measured using histomorphometric methods for 78 different areas in each screw. In the two screws that were extracted (screws A,B), the coating was 15 µm thick on average. Two additional screws with the same batch number were examined, one unused screw (C), and one screw that was screwed out immediately after the insertion (D). The thicknesses of the coatings were 40 and 36 µm, respectively.
Paper II

Five of the 28 screws that had been implanted for 6 or 12 weeks were considered to be loose when the rods were removed. All of these were uncoated screws, and the subsequent mechanical testing revealed a maximum pull-out resistance of less than 505 N for these 5 screws. For all other screws, both HA coated and uncoated, the maximum pull-out resistances were 1175 N or more. For the HA-coated screws, the maximum pull-out resistances all exceeded 1440 N. Thus, 5/14 standard screws were loose, compared to 0/14 of the HA-coated screws (Fisher’s exact test, p<0.05).

The maximum pull-out resistance was significantly higher for the HA-coated screws at 0 (p < 0.02) and at 12 weeks (p<0.01) when compared to the uncoated screws while there was no significant difference between groups at 6 weeks.

![Figure 8. Maximum pull-out load (average; * indicates a statistically significant difference)](image)

At 12 weeks “Stiffness A” was significantly higher for the HA-coated screws when compared to the uncoated screws while there was no significant
difference between the two screw types at 0 and 6 weeks. When stiffness was defined as the quotient between maximum load and the displacement at that load, “Stiffness B”, there was no significant difference between the treatment groups at any time point.

Energy to failure was significantly higher for coated screws when compared to the uncoated screws at all three time points.

Analysis of variance was performed for the pull-out resistance, and demonstrated a higher pull-out resistance for the HA coated screws at 0 weeks (p = 0.013) and 12 weeks (p = 0.014), while there was no significant difference at 6 weeks, i.e. similar p values to when using the Wilcoxon signed-rank test for the analysis.

Figure 9. Load-displacement curve for an HA coated screw after 12 weeks of implantation.
**Paper III**

In ten specimens, one to five of the twelve threads were missing after the preparation. Histomorphometric calculations could therefore not be made for bone-to-implant contact in 22/336 threads (13 HA coated and 9 uncoated threads), bone area inside the threads 21/336 threads (12 HA/9 uncoated), and bone area in the mirror area 27/336 threads (18 HA/9 uncoated).

The qualitative histologic analysis of the uncoated screws revealed large areas of soft tissue in the interface, giving the impression of bone resorption around the screws at both 6 and 12 weeks, while the HA coated screws mainly were outlined by bone at both 6 and 12 weeks. In minor parts of the interface of the HA coated screws, a thin (approximately 10-20 μm) layer of bone-stained acellular tissue could be observed.

**Figure 10.** One thread from uncoated screw after 12 weeks follow-up, demonstrating minimal bone-to-implant contact. Screw = A, Bone = B, Soft tissue = S. White line indicates 200 μm.
Figure 11. One thread from Hydroxyapatite (HA) coated screw after 12 weeks follow-up, with the screw outlined by bone. Screw = A, Bone = B, HA Coat = C. White line indicates 200 μm.

Surrounding the HA coated screws an acellular tissue other than the type described above could be observed after both 6 and 12 weeks. This tissue could form aggregations with a diameter of 100-200 μm, containing larger fragments resembling bone, but without its lamellar structure. This tissue did not seem to contain any collagen fibres when examined under polarised light. The distribution of this bone-resembling tissue was quite symmetric along the HA coated screws. Especially in the 12-week group areas of polarisation were intermingled with the non-polarising tissue. This bone-resembling tissue could not be found around the uncoated screws.

The histomorphometric examination demonstrated a bone-to-implant contact of 69±10 % for the HA coated screws and 18±11 % for the uncoated implants after 6 weeks implantation (p<0.03). After 12 weeks implantation, the bone-to-implant contact was 64±31 % for the HA coated and 9±13 % for the uncoated implants (p<0.02). The amount of bone in the inner thread area after 6 weeks was 68±6 % for the HA coated and 47±22 % for the uncoated screws (p< 0.05),
and after 12 weeks 56±31 % for HA coated and 30±29 % for the uncoated screws (p<0.05). In the mirror area there was 67±5 % bone for HA coated and 49±24 % for the uncoated screws after 6 weeks (N.S.), and 48±28 % for the HA coated and 37±32 % bone for the uncoated screws after 12 weeks (N.S.). For these calculations, the Wilcoxon signed-rank test was used. Histomorphometric data were also evaluated using three-way analysis of variance with similar results.

The bone-resembling tissue could only be found surrounding the HA coated implants, and the amount was not significantly changed from 6 to 12 weeks.

**Paper IV**

The mean insertion torque was 76±41 Ncm for the uncoated screws, 56±22 Ncm for the partly HA coated screws and 122±74 Ncm for the fully HA coated screws. The insertion torque for the fully HA coated screws was significantly higher than the torques for the uncoated screws and the partly HA coated screws, respectively. There was no significant difference between the uncoated and the partly HA coated screws.

The extraction torque exceeded the upper range of the torque wrench (600 Ncm) for 0/32 screws in the uncoated group, 3/24 screws in the partly HA coated group and 18/23 screws in the fully HA coated group. These values were set to 600 Ncm for the statistical analysis. The calculated values of mean extraction torque were 29±36 Ncm for the uncoated group, 447±114 Ncm for the partly HA coated group and 574±52 Ncm for the fully HA coated group. There were significant differences between all three groups (p<0.001). These differences were significant also when the average extraction torques for all four screws in each patient were analysed.
Figure 12. Maximum extraction torques for the three types of screws. Each symbol indicates one screw. The upper limit of the torque gauge manometer is 600 Ncm.

The purchase of the screw expressed as the maximum torque increased from insertion to extraction for 0/32 screws in the uncoated group, 18/19 screws in the partly HA coated group and 19/19 screws in the fully HA coated group. The maximum torque decreased from insertion to extraction for 31/32 screws in the uncoated group, while the torque was unchanged for one screw. There was no difference in extraction torque when analysed by age or by level. Some of the fully HA coated screws were difficult to extract with a screwdriver, while there was no problems with the extraction of uncoated and partly HA coated screws.

At the radiological evaluation, wide radiolucent zones surrounded 8/32 uncoated screws; thin radiolucent zones surrounded 9/32 uncoated screws and 1/28 partly HA coated screws. No radiolucent zones were seen in the fully HA coated group. There was a significant difference in presence of zones between the uncoated group and the partly and fully HA coated groups (p<0.001), while there was no significant difference between the partly HA coated group and the
fully HA coated group. A thin sclerotic zone surrounded all wide radiolucent zones. Several, but not all, of the thin radiolucent zones had a sclerotic zone. The fusions were radiologically healed in 14 of the 21 evaluated patients, while five fusions were assessed as not healed, and two as doubtful healing. Of the fusions that were radiologically not healed, 2/5 were assessed as non-unions during surgery, while the other three were judged to have healed. The two doubtful healings and all 15 radiologically healed were also assessed as healed during surgery. Both the cases that intraoperatively were assessed as non-unions were in the uncoated screw group, and had zones surrounding 1/4 and 2/4 screws, respectively.

**Paper V**

**Clinical study.** All screws were judged to be correctly placed in the pedicles and the vertebral bodies. No hardware failures could be detected. On the radiographs taken before extraction of the instruments, thin radiolucent zones could be noted surrounding 10/84 screws, and wide zones surrounding 8/84 screws. No zones could be noted in the five screws where no record of extraction torque could be taken. The mean extraction torque for the screws with radiolucent zones was 16±10 Ncm, while the mean extraction torque for the screws without zones was 403±220 Ncm (p < 0.0001). There was no difference in extraction torque between the screws with wide radiolucent zones and screws with thin zones. In the two patients were the fusions had not healed, 3/8 screws demonstrated radiolucent zones.

In the eight patients where uncoated screws were used, radiolucent zones could be noted in seven patients and 17/32 screws.
Experimental study – Mechanical evaluation. No misplaced screws could be detected. Radiolucent zones 2-3 mm wide could be noted surrounding 5/28 screws. The mean maximum pull-out resistance for the screws with radiolucent zones was 243±156 N, while the mean pull-out resistance for the screws without zones was 2214±578 N (p = 0.0006). None of the screws with radiolucent zones had a pull-out resistance exceeding 505 N, while the pull-out resistance for the screws without zones was 1175 N or more.

Figure 13. Radiograph of sheep spine, demonstrating radiolucent zones surrounding screws in L2-L3 (upper).

Experimental study – Histomorphometric evaluation. All screws were judged to be correctly placed. The radiological examination revealed radiolucent zones 1-4 mm wide surrounding 9/28 screws. The mean bone-to-implant contact was 8±9 % (range 0-21) for the screws with radiolucent zones, and 55±29 % (range 4-94) for the screws without any zones (p = 0.0002). The mean amount of bone in the thread and mirror area was 16±21 % (range 0-53) for the screws with radiolucent zones and 65±13 % (range 18-79) for the screws without any zones (p < 0.0001).
GENERAL DISCUSSION

These studies originated from the observation of radiolucent zones surrounding pedicle screws. In most studies of pedicle screw fixation, the frequency of screw loosening is low. Contrary to this, we could quite often note radiolucent zones surrounding the screws of spinal instrumentations. When special views were included in the radiographic examination, 53% of the uncoated stainless steel screws in the clinical part of the study demonstrated radiolucent zones (paper V). The very low frequency of screw loosening in several other studies could probably be explained by the use of other criteria for screw loosening, such as dislocations of the screws, or by the fact that most of these studies were retrospective, with varying standards for the radiographic examinations. In the present study (paper V), the screws with radiolucent zones demonstrated lower extraction torques and pull-out resistances as well as lower amounts of bone surrounding the screws and inferior bone-to-implant contact. Another interesting fact was that the presence of a radiolucent zone always indicated that the screw was loose, meaning that there were no false positive findings. With the criteria used, a radiolucent zone was a good indicator of screw loosening.

Various kinds of animals have been used as models for the study of the spine. Small animals such as rodents are difficult to use for studies of instability and fusion of the spine [48]. The sizes of the available instrumentations also make it necessary to use larger animals for studies of spinal implants. The size of the mature bovine and porcine spines are too big to be used as models for spinal implants [12, 68], and due to the rapid growth of the spines of younger individuals they could not be used for long-time studies. Sheep and dogs have been the most commonly used animals, and there are several studies of spinal implants with ovine or canine models [44, 45, 48, 73, 87]. Mature mini-pigs have also been used [8].

Based on the biomechanical similarities between ovine and human spines, the sheep spine has been described as a reasonable anatomical model for instrumentation affecting the thoracic and lumbar spine [94, 95]. According to
Kotani et al, the sheep spine is more similar to the human spine in terms of cancellous bone quality, size, pedicle diameter and transverse processes when compared to the canine spine [48]. Based on this data, a sheep model was chosen for the experimental part of the study.

Different methods were used for the evaluation of the anchorage of screws in the experimental and clinical parts of this study. In both the experimental and clinical studies, the screws had been subjected to loading for various times, and the purpose of the tests was not to resemble the mechanisms of loosening, but to assess the fixation of the screws after loading. It remains controversial whether pull-out resistance or extraction torque best reflects the purchase of pedicle screws. The screws used in the present studies were prevented from rotation by firm connections to the rods. Therefore, pull-out resistance was chosen for testing in the experimental study. In the clinical situation, testing of pull-out resistance was impracticable, and extraction torque was used for the evaluation.

The first clinical study (paper I) demonstrated a very good fixation of the hydroxyapatite (HA) coated screws, when used in only one of the two instrumented levels in a four-screw construction. The loosening mechanism of pedicle screws has been described as a cyclic caudocephalad toggling [65, 100]. If loosening of the uncoated screws occurred while the HA coated screws still had a sufficient anchorage, this could perhaps concentrate the toggling to the uncoated screws, thus protecting the HA coated screws from loosening. To be clinically more relevant, an increased purchase of pedicle screws should comprise all screws in the instrumentation. For the second clinical series (paper IV), four screws of the same type were used in each instrumentation. Due to the problems with extraction of the fully HA coated screws in the first clinical series, a screw that was partly coated with HA was included in the second series.

For almost all of the studied variables, hydroxyapatite (HA) coated screws demonstrated superior results in these studies. There are no previous clinical studies where the HA coated pedicle screws have been compared to uncoated screws concerning purchase and radiological appearance. In two earlier
experimental studies of HA coating for pedicle screw fixation, unloaded models have been used with differing results [73, 87]. For other implants, as stated by Albrektsson, there seems to be no experimental evidence of any difference in fixation strength at one year after insertion [1].

Many different factors could be considered as explanations of the results in the present studies. The loading of the screws is most probably an important factor. In studies by Søballe et al, loading of implants resulted in an increased amount of bone ingrowth when compared to unloaded implants. After 4 weeks of loading, the ultimate shear strength of the HA coated implants had increased three-fold as compared to unloaded implants, while there was no effect of loading on titanium implants [81, 82].

The positive effects of the HA coating in the present studies may also be related to the characteristics of the bone bed in the pedicle and the quality of the bone in the animal model used, as the bone response may differ between different bone beds [36, 37].

All the HA coats in the present studies came from the same manufacturer. Several batches were used, but the specifications from the supplier were similar, as also the processes. In Gottlander’s studies of several HA coats [32], the only two coats that showed significantly more bone-to-implant contact than commercially pure titanium originated from the manufacturer that did the coats used in the present studies. The type of coat used could be an important factor for the results of the present studies, and pedicle screws with HA coats from other manufacturers may give other results with respect to fixation and bone-to-implant contact.

There are considerable differences in surface roughness between HA coated and uncoated screws. A four-fold increase in surface roughness of plasma-sprayed HA coated implants when compared to machined titanium implants has been described [93], and the surface roughness of stainless steel is less than that of machined titanium. Surface roughness can influence the tissue response to an implant, such as the orientation of fibrous tissue and bone ongrowth [67], and therefore give long-term effects on fixation. Regarding the mechanical effect of
surface roughness only, it could cause the higher insertion torque for fully HA coated screws in paper I & IV. It could also cause the higher pull-out resistance for the HA coated screws in paper II that were tested immediately after application (0 week group). At follow-up, however, there was a marked increase in purchase over time for the HA coated screws, compared to the decrease over time for the uncoated screws (paper I & IV). A similar tendency could be noted for the pull-out resistance between 6 weeks and 12 weeks in paper II, although not significant. Therefore, the higher surface roughness of the HA coated screws is unlikely as a direct mechanical cause for the better results at follow-up.

The plasma-sprayed HA coating increases the diameter of the coated screws with an average 80-90 μm when compared to the uncoated screws. This means a relative “oversizing” of approximately 2% of the HA coated implants that could contribute to the higher insertion torque and higher pull-out resistance at 0 weeks. For the same reasons as for surface roughness, oversizing is not likely to have caused the better purchase and bone apposition at follow-up.

Contrary to most experimental studies, the preparations of the holes for the pedicle screws were made with a pedicle probe (papers II & III). In most experimental studies, the holes have been prepared with sharp drills, often with increasing diameters, in order to maintain a good quality of the bone surrounding the implant. The probe used in the present studies is a blunt instrument with a spoon-like expansion of the tip. This probe was used in order to resemble the clinical situation. This causes compression of the bone surrounding the probe, and the bone resembling tissue found close to the HA coated screws (paper III) probably consisted of bone that was destructed during the preparation. After 12 weeks of implantation, polarising areas could frequently be seen intermingled with the bone resembling acellular tissue around the HA coated screws, while the acellular tissue could not be found at all around the uncoated screws. One possible explanation is that the acellular tissue, consisting of bone debris, was remodelled to lamellar bone around the HA coated screws, but resorbed around the uncoated screws.

In the present studies, hydroxyapatite coating of pedicle screws resulted in an improved fixation and better bone apposition. The mechanism of the improved
fixation, however, is not clear. It could be caused by a direct chemical bond between bone and the plasma-sprayed HA of the implant. The close contact between bone and implant could also cause a mechanical bonding. Some authors have proposed that the fixation of HA coated implants is caused by a chemical bond [30]. In other studies, dissolution of individual grains of the implant surface gave a rougher surface than originally implanted, and mechanical interlocking could not be eliminated as a contribution to bone-HA bonding [16, 24]. Both in the experimental and clinical parts of the present studies, similar observations were made. In some cases the fixation of the screws increased after a short time of implantation, making it very hard to adjust the screws after only a few minutes. This rapidly increased fixation probably could be caused by chemical factors as well as mechanical.

Also after long-term implantation there were some problems with the extraction of the fully HA coated screws (paper I). These problems diminished with increasing experience of the extraction procedure of the fully coated screws, but the extraction could be troublesome in some cases. This could be managed by varying the extent of the HA coat, as demonstrated in paper IV. The further increase in purchase with fully coated screws may be useful for certain indications, such as surgery for tumours of the spine or in patients with osteoporosis.

The HA coating used in the present studies appears to be effective for improving the anchorage of pedicle screws also in older patients. In the clinical part of this study, there was no difference in the purchase of HA coated screws between older and younger patients, with a very good purchase even in the oldest patients (paper IV). This is consistent with the results of experimental studies [23, 78].

For all the present studies, the HA coated screws were compared to uncoated stainless steel screws. When the studies were initiated, there was no titanium pedicle screw system available in a size that was appropriate for use in sheep, and stainless steel was used. The favourable biocompatibility of titanium has been demonstrated mainly for commercially pure titanium and it has not been
shown that titanium alloy, used for pedicle screw instrumentations, is as well accepted in bone as is commercially pure titanium. In spite of this, it is an interesting question whether uncoated titanium would have performed superior to uncoated stainless steel.
CONCLUSIONS

- Radiolucent zones are good predictors of loosening of pedicle screws.

- The frequency of radiolucent zones surrounding the screws in spinal instrumentations is higher than previously described.

- Hydroxyapatite (HA) coating of pedicle screws demonstrates improved fixation, better bone-to-implant contact and higher amounts of bone surrounding the screws in a loaded animal model.

- In spinal surgery, HA coating of pedicle screws improves fixation of the screws and reduces the frequency of radiolucent zones surrounding the screws.

- The purchase of HA coated pedicle screws can be adjusted by varying the extent of the HA coat.
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