# BONIT
# A Review of the published literature to 2007

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## Executive Summary

Animal studies and clinical trials have provided impressive proof of the efficacy of BONIT coatings. Accelerated implant healing, increased bone formation and improved mechanical implant anchoring have been observed especially in the early post-implant phases. This means that the load bearing properties of the implant are robust at an early stage BONIT® coatings are completely resorbed in a controlled way (approximately six to twelve weeks following implantation) and are simultaneously replaced by bone. The coatings are well tolerated and no inflammatory or rejection processes have been reported. This paper provides an analysis and summary of the published literature to date.

## 1. Introduction

The purpose of this paper is to describe the properties and clinical applications of a novel solution deposited calcium phosphate coating, BONIT. Calcium phosphate coatings have been used on dental and orthopaedic implants at the bone/implant interface for over 20 years. They are defined as ‘bioactive or osteoconductive’ coatings. The first reported use was for in the fixation of dental implants in 1971[1] . The first orthopaedic implants to be coated were femoral stems[2] but subsequently reports have been published regarding their use of on acetabular cups[3], tibial and femoral knee components, external and internal fixation screws and more recently pedicle screws for spinal fixation[4]. The purpose of these bioactive coatings is to enhance the bonding of the device to bone. A device made from a calcium phosphate ceramic alone would not be sufficiently strong and tough to be used in a highly loaded application such as for hip or knee replacement. However when used as a coating they confer excellent properties of biocompatibility to the metal implant surface and cause bone to grow directly against it, rather than with the normal intervening (and weaker) fibrous membrane which is present when foreign materials are implanted in bone.

The main clinical advantages conferred by these coating for orthopaedic and dental applications relates to the increased stability of their fixation in the short/medium term[5] . It has also been reported that these bioactive coatings used for fixation of hip and knee joints reduces the pain felt by a patient during rehabilitation and indeed shorten the overall rehabilitation time. It has been shown that in the longer term a bioactive coating will either resorb or be remodelled and disappear[6]. The time scale this happens in depends on the types of calcium phosphate, how it has been deposited and the clinical situation. Generally as the coating resorbs, the bone steadily grows to fill the gap remaining and the implant remains well fixed. This does mean, however that a implant should not rely solely on the calcium phosphate for fixation but should have good primary stability as well.

## 2. Coating Composition and Manufacture

As mentioned in the introduction, the BONIT coating is manufactured from a solution deposition route. This confers certain advantages which are discussed below.

There are several different types of calcium phosphate coatings which have been investigated and used clinically. Hydroxyapatite (HA) is one type ($Ca_3 (PO_4)_6 (OH)_2$) and there others which are less frequently used, such as Bioglass™, tri-calcium phosphate (whitlockite), and fluorapatite. Traditionally these coatings have been applied by plasma spraying techniques[7]. In this method the hydroxyapatite granules are propelled towards the implant surface using gas plasma at approximately 20,000° C. The supersonic speed of the gas (usually an ionised mixture of hydrogen and argon) also causes frictional surface heating of the granules which locally melt and then solidify onto the surface and each other. Generally the coatings are between 55-200 microns thick, depending on the manufacturer (if any thinner it is it is difficult to ensure uniform coverage using plasma spraying) and they always have some inherent porosity (approximately 30%) due to the incomplete interparticle packing. The plasma sprayed coatings are formed into a combination of completely melted, partially melted, and unmelted particles. This causes them to be inhomogeneous (physically and chemically) with specifications which are relatively broad compared to solution deposited coatings.

Air or vacuum sprayed coatings are available and the latter is said to have more closely controlled properties however any clinical benefits arising from this are anecdotal. Some of the features of plasma spray coatings are shown in Table 1

Table 1 Features of plasma sprayed HA coatings

| **Feature** | **Strength / Weakness** |
|---|---|
| Long term clinical use | Straight forward regulatory pathway |
| Many suppliers | Cost competitive |
| Line of sight process | Difficult to achieve uniform thickness |
| High temperature | Inhomogeneous |
| Inhomogeneous | Variable absorption of coating |

Solution deposited coatings are also available. BONIT is the main example but there at least two others which have been sold in Europe (PeriApatite[1] and Rainbow Coat[2]). The metal implant is held in a tank containing a recipe of supersaturated soluble precursors of the coating. By the manipulation of pH, temperature and concentration the calcium phosphate is encouraged to mineralise directly onto the implant surface (in the case of BONIT, encouraged using an electrophoretic effect.) This is a low temperature process which produces homogenous chemistry and uniform thickness coatings. It is particularly appropriate for implants with more complex surface topography. It should be noted, however that the inherent strength of such coatings is lower than with a plasma sprayed coating because deposition is a passive, low energy process. This has not appeared to give any clinical problems since the coatings are thin (approximately 20 micron). Such coatings have been used clinically on hip and knee prostheses since 1995. The use however, has been less widespread than plasma sprayed coatings. Table 2 shows some of the main features of solution deposited coatings.

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[1] Stryker

[2] Isotis

Table 2 Features of solution deposited coatings

| **Feature** | **Strengths/Weaknesses** |
|---|---|
| Low temperature and chemical process | Homogeneous and controlled |
| Will coat any surface the solution touches | Not line-of- sight |
| Thin | Less chance of debonded material |
| Simple process | Reduced cost |
| Homogeneous | Predictable rapid resorption |
| Less widespread clinical use | Need market positioning |

Although clinical results in orthopaedic applications have been good with plasma sprayed coatings, many clinicians would prefer a coating that fully resorbs within a short time scale once implant stabilisation has been assured. Ideally coating dissolution is concurrent with new bone growth at the implant surface. These solution deposited calcium phosphate coatings answer this demand and have been to be found to be safe and efficacious. However, few have been taken through the rigorous clinical and safety evaluation needed to be established on the commercial market. This paper provides a thorough review of BONIT[8] (DOT de), a brushite, electrochemically deposited coating which has been used with success in the clinic since 1995.

Process

The deposition method for BONIT uses electrochemical energy to encourage the coating which deposits from solution to adhere to the metal surfaces. The metal surface normally has a pre-coat of plasma sprayed titanium which roughens and provides a first layer of porosity for the bone ingrowth which is encouraged by the BONIT top-coating – see patent WO 0020 5862 (A1).

## 3. Properties

### a. Chemistry and general properties

BONIT coatings consist of a type of calcium phosphate called brushite. The formula for brushite is $CaHPO_4.2H_2O$, which has a ratio of Ca/P 1.0; brushite is known to be formed naturally in the body as an intermediate stage during the calcification of new bone [9]. BONIT coatings are 10-15 micron thick (see Figure 1), and consist of millions of small, plates-like crystals (10-20 micron) (see Figure 2);

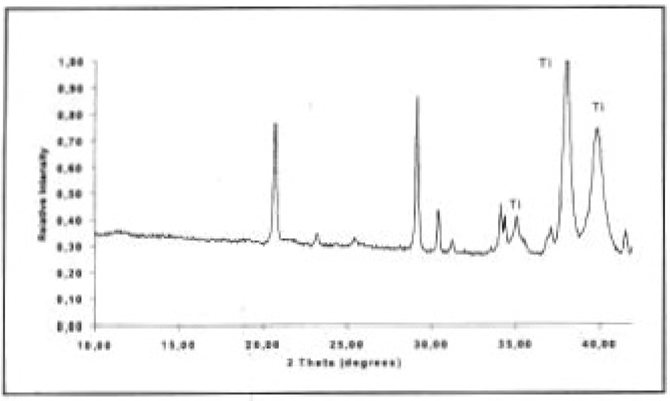


Figure 1 Brushite XRD[5]

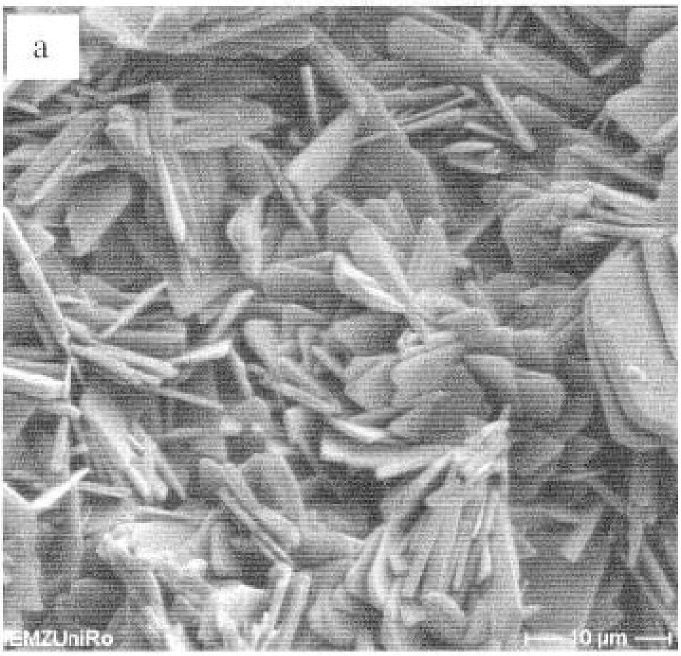


Figure 2 Brushite crystals found in BONIT[5]

Metal ion release into the body is often considered to be an undesirable property of the standard metal alloys used in orthopaedic and dental implants. BONIT coating has the possibility to inhibit this by acting as a passive layer and is reported to reduce the anodic metal ion dissolution from stainless steel and titanium-aluminium-vanadium alloys even though the BONIT is approximately 80% porous. Experiments were performed to investigate this effect using potentiostatic measurements on coatings which had been deposited for different amounts of time. The coating deposition time was found to influence the effect. It was found up that below a 3 minutes deposition time the anodic current of the substrate actually increased compared to the uncoated control (due to the presence of pits in the coating which created points with a high current density, promoting selective metal ion dissolution). Longer deposition periods of up to 20 minutes produced a thicker coating with an associated decrease in anodic current and dissolution and thus potential dissolution protection.

The BONIT coating is designed to completely disappear after 6-12 weeks in vivo (compared to plasma sprayed hydroxyapatite coating which are intended to remain in situ for years rather than months. Often partially remnants of plasma spray coatings can be found up to 5 years post-implantation) For plasma sprayed coatings the amorphous regions tend to dissolve preferentially and this can occasionally allow the release of small crystalline particles which ideally become encapsulate in the newly growing bone. There are however risks associated with such released particles if they are not encapsulated. It has been reported that particles of hydroxyapatite which became detached from poorly manufactured hydroxyapatite coatings which were too porous or too weak, become trapped in the metal- polyethylene bearing of hip joints. This led to scratching of the metal femoral head and accelerated polyethylene wear and failure. Others have reported localised inflammatory responses to released hydroxyapatite particles which could also cause premature failure due to excessive osteolysis and granulation at the fixation. These negative effects are however rare and have only been reported on a case basis rather than as a regular feature of large clinical data sets.

Electrochemical and other solution coatings are more homogeneous with a high surface area. The small crystals of brushite can readily dissolve in physiological environments (especially in the decreased pH environment at the sites of wound healing) and this tends to be at a more uniform rate. Particles do not appear to be released or mediate any activated macrophage or giant cell mediated inflammatory reactions[1].

## b. In Vitro

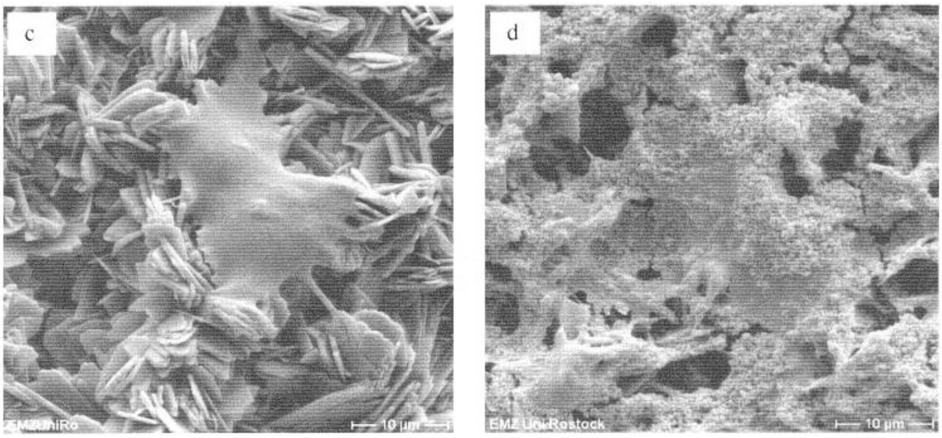
Various laboratory studies have been performed to characterise the coating and thus understand its function. The next section describes the main studies and results.

### Wettability

The coatings are highly wettable because of their very fine nano-scale structure[10] Wettability may enhance cellular adhesion and tissue ongrowth in vivo. In order to investigate this, the contact angles of polar and apolar solvents on hydroxyapatite, brushite, monetite and uncoated titanium samples were measured and compared. It was found that the value was >90 for all uncoated substrates but lay between 59 and 81 degrees the coatings i.e. the calcium phosphate was more wettable than the bare metal. This was due to both the chemistry and the surface roughness. The latter effect was clearly apparent. Surface porosity also varied with the coating surface roughness, the roughest being the electrodeposited hydroxyapatite. This produced the lowest contact angle of 59 degrees. The brushite value was also lower than the bare metal i.e. 62-64 degrees.

### Immersion in culture medium and osteoblast responses

In order to study in vitro behaviour, 20 micron thick coatings[11] on titanium discs with a range of solubilities were prepared. Their starting or as-received composition was brushite with <5% HA and it could be seen that their crystalline morphology was in the form of vertically aligned plates).These samples were designated B/HA. Some of these coatings were then transformed to either monetite (M) or (HA). All the samples were immersed in culture medium (D MEM) without cells for 48 hours and it was found that new crystals of calcium phosphate (CaP) were spontaneously deposited on the B/HA but not on the M/HA or HA surfaces. Good on-growth of osteoblastic MG-63 cells on the coated surfaces was found in all cases (see also reference 5) but the cells grown on B/HA were partially covered in the newly precipitated crystals of CaP (Figure 3, image (d) below).

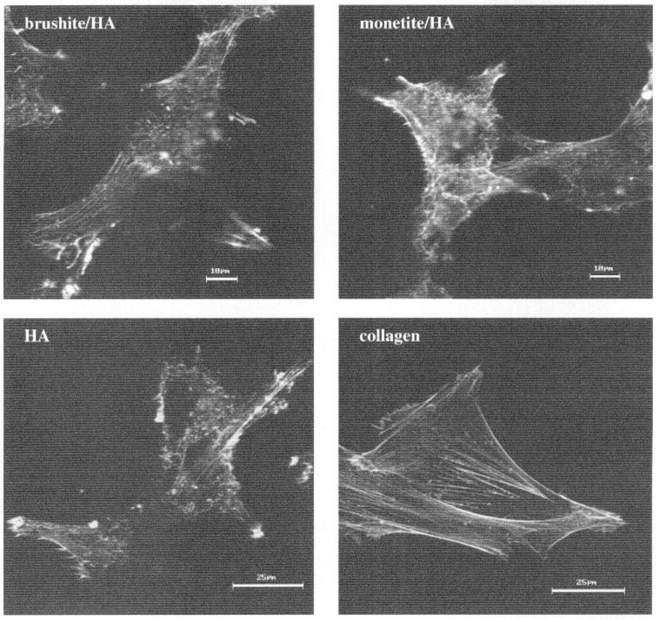


micrographs of (a) a B/HA composite surface, and (b) after immersion in DMEM for 30 h. In (c), B/HA composite surface cultivated lls for 8 h, and in (d) for 30 h. Note the new precipitated, finely structured CaP on the surface of B/HA composite (b, d).

Figure 3

## Osteoblast Responses

Further degradation studies were performed [12] in vitro. Coated samples, 15-20 microns thick, were soaked for 2,7,14 and 28 days in an artificial bone fluid. In addition, proliferation and phenotype tests (studying the presence of both collagen type 1 and osteocalcin) were performed using human foetal osteoblasts cultured on uncoated and BONIT coated titanium samples. These markers are indicators of the potential for future bone ongrowth. The markers were up-regulated on the coated versus the control samples. Furthermore, osteoblast[13] (MG-63 osteosarcoma cell line) were cultured at a density of $3x10^4$ in D MEM plus 10% foetal calf serum on discs of titanium coated with a) BONIT 20 micron thick b) Monetite or c) Hydroxyapatite. The actin cytoskeleton of the cells was analysed after 48 hours, using the marker phalloidine-TRITC (Sigma) and confocal scanning microscopy. Pronounced stress fibres were shown on all surfaces tested (Figure 4); again this is a good indication of the potential of the BONIT surface coatings to encourage the ongrowth of well-organised, on-grown new bone.



M images of the actin cytoskeleton of MG-63 cells on brushite composite and monetite composite as well as pure HA, (
ol). Note that cells reveal a spread morphology and actin stress fibres on all modified surfaces. LSM 410 (Carl Zeiss).

Figure 4

In addition, these experiments showed a good correlation between the in vitro and in vivo results[14]

In another experiment, the effect of the coating structure, phase degradation and re-precipitation of the coatings on osteoblasts showed that BONIT with reduced HA to be a precursor for bone[15] formation. Similar high solubility CaP phases are found in vivo, during the initial stages of bone healing, and they provide favourable conditions for osteoblast differentiation.[16]

## Electron Microscopy

Scanning electron microscopy (SEM) and X Ray Diffraction (XRD) were used to characterise the solubility of the BONIT coatings after soaking samples in Tris buffer. The measures of

- Weight loss
- Ca/P ratio
- X Ray Diffraction or XRD (measuring composition and crystalline before and after soaking)

were used. In addition osteoblast cell adhesion using a collagen substrate as a control surface was assessed before and after soaking.The results are shown in Figures 5, 6 and 7

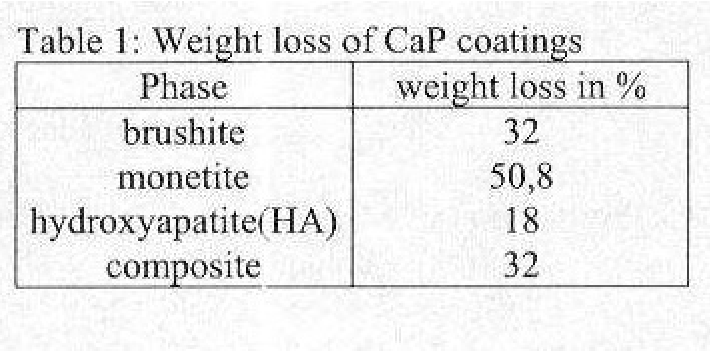


Table 1: Weight loss of CaP coatings

| Phase | weight loss in % |
|---|---|
| brushite | 32 |
| monetite | 50,8 |
| hydroxyapatite(HA) | 18 |
| composite | 32 |

Figure 5 Weight loss after soaking

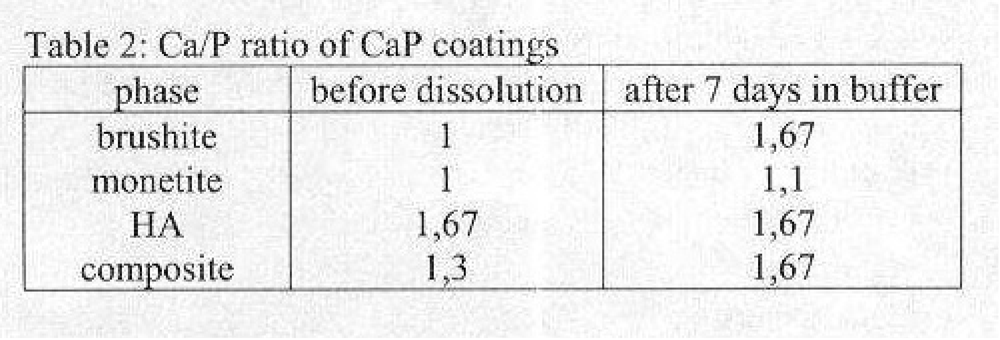


Table 2: Ca/P ratio of CaP coatings

| phase | before dissolution | after 7 days in buffer |
|---|---|---|
| brushite | 1 | 1,67 |
| monetite | 1 | 1,1 |
| HA | 1,67 | 1,67 |
| composite | 1,3 | 1,67 |

Figure 6 Coating composition after soaking

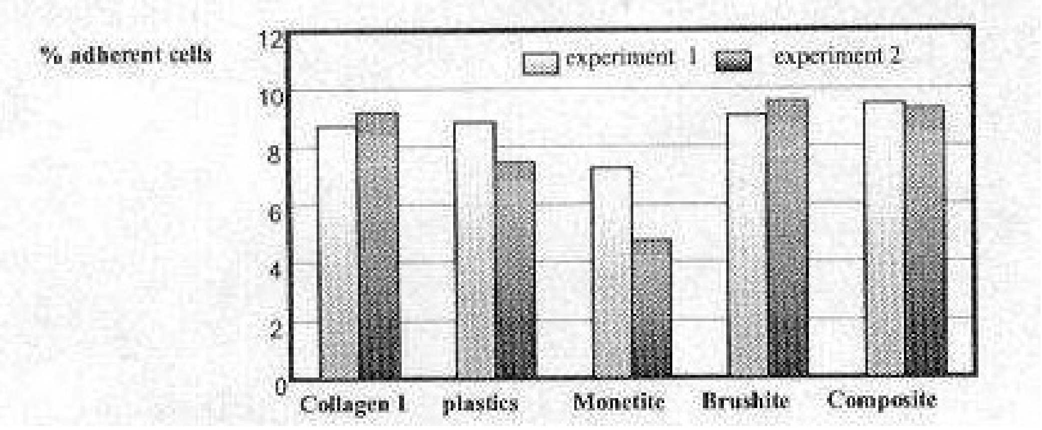


Figure 7 Osteoblast response to coated surfaces compared to a collagen control.

It can be seen in Figure 5 that the solubility of the brushite (BONIT) coating, indicated by its weight loss, was considerably greater than for hydroxyapatite. This is confirmed by the observation that the Ca/P of the hydroxyapatite remained unchanged but the calcium content of the brushite decreased (Figure 6). All surfaces produced surfaces which were as biocompatible as collagen alone resulting in comparable numbers of adherent osteoblasts (Figure 7)

### Antibiotic Release

The suitability of BONIT coating as a carrier for antibiotics has also been assessed[17].Two groups of samples were prepared. One had a plasma spray titanium surface; the other a hydroxyapatite surface. These were then additionally coated with BONIT loaded with gentamicin. Antibiotic release was assessed by eluting the samples in a phosphate buffered saline, pH 7.2 at 37 degrees, for 1, 2, 8, 24, 48 and 72 hours. The eluted gentamicin was measured using a fluorescent polarisation immunoassay. The release was rapid from both surfaces, reaching a peak concentration at 30 minutes. The hydroxyapatite coated surface showed the most prolonged release profile (90% was released after 72 hours elution time). In the opinion of the authors, the amount released (3 mg/cc) was higher than that normally released from a 2mm thick bone cement mantle (Palacos plus Refobacin 2.5 mg/cc). This study showed that BONIT could potentially be used to facilitate the prophylactic release of antibiotics from non-cemented implant surfaces.

## c. In Vivo Studies

A number of interesting studies have been conducted in animals to demonstrate the safety and efficacy of the BONIT coatings. The animal models have included porcine, baboon, canine and ovine. Most frequently the effect of BONIT has been investigated by comparing its bone fixation potential with the control surface of plasma sprayed titanium coating (PST) which is used as a pre-coat for BONIT. These experiments and their results are described in the sections below.

### Porcine

The Transcortical Göttingen Minipig Model was validated[18] using both intercondylar and intertrochanteric implants in both femora using 30 pigs (n=80 in 20 females and n=10 in 10 males). It was found that the implant location did not affect the results and a good statistical analysis was possible using these large data sets.

This model was then used to evaluate the effect of roughness and the effect of BONIT[19]. Four different (A: Glass bead blasted, B: Sand blasted, C: Titanium plasma spray, D: Titanium plasma spray plus BONIT) types of surfaces (n=20 for each) were implanted in mini-pigs, as described in reference 18, for 12 weeks. These samples had roughness (Ra) ranging from 0.8 to 28.4 microns. (with increasing roughness from A to C and D).

After sacrifice, 10 explants were processed, sectioned and studied histologically. Pull-out tests were performed on the remaining 10 explants. It was found that Type A showed bone ongrowth of 1.9% (±1.1), Type B 10.5% (±3.6), Type C 22.4% (±4.5) and Type D 48.8% (±4.5). This variation was related to the influence of surface roughness which enhances bone ongrowth. Furthermore, the addition of the BONIT coating (comparing C and D) provided a 26% improvement over the comparable uncoated surface. The mechanical and histomorphometric results were similar for both the intertrochanteric and the intercondylar implantation sites. Histologically, it was founds that bony trabeculae developed parallel to the surface of the implants for Types A and B; whereas the trabeculae grew directly onto the surface of the implants for Types C and D. This type of direct bone ongrowth should result in a more stable fixation which would resist shear forces in vivo. It can be seen (Figure 8) that the BONIT showed the highest strength interface thus confirming this effect.

| Group | Shear-strength [N/mm²] | Stiffness [N/mm] |
|---|---|---|
| A | 0.7* ± 0.3 | 11.6 ± 7.8 |
| B | 3.2* ± 0.6 | 13.3 ± 2.1 |
| C | 6.5* ± 1.5 | 10.5 ± 4.6 |
| D | 7.3 ± 1.9 | 11.1 ± 3.2 |

Figure 8: Results of the pull - out tests and the stiffness analysis. (Statistical significant (*) differences were seen with the shear – strength between all groups, except for group C and D. Regarding the stiffness no statistical significant differences were seen.)

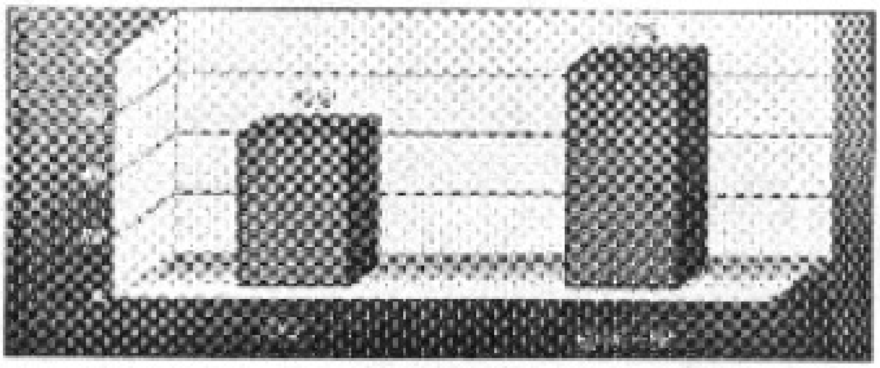
In a subsequent study, mini-pigs[20] (n=18) were implanted with alumina headed, femoral hemi-prostheses fixed to the bone using three different coatings i.e. a) porous plasma sprayed titanium porosity 20-40% b) plasma sprayed titanium as above + BONIT and c) poly (dl-lactide) plus a bone morphogenic protein, BMP-2 ((0.4 microgram per microlitre) (n=6 per group)). A further minipig study showed that BONIT coated on a titanium plasma sprayed substrate has the capacity to cause new bone to fill gaps between the uncemented prostheses and bone bed even in the absence of BMP, but it does not improve bone density [21] A further comparison of different surfaces and their effect on osteointegration in minipigs showed that BONIT significantly increased the amount of new ingrown bone (48.8% compared to 22.4% with a titanium plasma sprayed surface alone (see below))

| Surface | Bony Ingrowth | |
|---|---|---|
| Glass beaded | + | 1.9% |
| Sand blasted | ++ | 10.5% |
| TPS | +++ | 22.4% |
| TPS & BONIT | ++++ | 48.8% |

It was also noted that increased surface roughness of an implant placed in bone resulted in improved osteointegration[22 23].

Several studies in pigs have found that BONIT also performs effectively as a fixation for dental implants. The first, in 1998, studied the response to 6 implants (stage Pitt Easy Bio-Oss system) in the mandible and maxilla of pig[24] (14mth old, Land Race) After 3 months the pigs were sacrificed and segmental osteotomies were prepared with 3 cross-sections taken from each implant for histology. Subsequently, in 2001, 8 implants[25] 4.9mm x 8 mm, n=4 plasma spray control vs. n=4 BONIT (15-20 micron thick, Ca/P 1.1 +/- 0.1) were studied in a similar model. In both studies[24] the coating appeared to have totally dissolved or resorbed at 3 months; no remnant of the BONIT could be seen using a light microscope. Push-out tests were also performed to assess the strength of the resulting bone/implant interfaces. The removal torque for the mandibular implants was 160 Nm. This was higher than that found for the maxillary implant/bone interface, probably due to the presence of the compact mature bone seen directly in contact with these implants; the removal torque for the maxillary implants was 60 +/- 3.46 Nm and direct apposition of both compact and (weaker) cancellous bone could be seen. No multi -nucleated or other inflammatory cells were present which demonstrates the good biocompatibility of the coating and its resorption products. The resorbed coating clearly was substituted by new bone.

In the second study [25] the coating resorbed more than 99% and even greater bone apposition (73.0 +/- 6.2 % versus control 49.8 +/- 16.4 %; p= 0.009) was found. Again, no macrophage or osteoclastic activity was observed in the region of the BONIT coating again confirming that there is no negative inflammatory response to BONIT as it resorbs.



[26] Figure 5 : diagram showing the BIC at the TPS control implants and the Bonit-FRR coated implants after 6 weeks of implantation

Figure 9

Figure 9 above shows the bone apposition data obtained in the pig studies discussed above [24, 25]

Baboon [27]

The SB Charité human-sized lumbar disc replacement was assessed in a baboon spine model. The implants had polyethylene bearings (7.5mm thick) and were made from a cobalt-chrome alloy coated with plasma sprayed titanium plus BONIT to assist fixation to the end-plates. These titanium plasma spray coatings consisted of a pre-coat (90 micron) with a further 180 micron thick layer over the top. Such a titanium coating is intrinsically porous, with a pore size of 5-300 microns, surface roughness Ra of 35 microns and reportedly have a pull-off strength >45 MPa. The BONIT was applied over this coating to further enhance fixation. In the study, seven (7) mature baboons, 35-40 kg were implanted with the disc replacements, using an anterior transperitoneal approach, after a complete discectomy L5-L6. They were sacrificed six (6) months post-operatively. Radiography, biomechanical analysis and histomorphometry were then performed. L3-L4 and L5-L6 were mechanically tested as intact ligamentous spinal units (with the soft tissue and muscle having been removed) n=10 spinal units were tested and each test was repeated five (5) times. In these tests the range of motion was assessed under axial compression (500N) rotation (+/- 4 Nm with 150 N pre-load) and flexion/extension (+/- 4 Nm). The results were compared with intact spinal units and are shown below.

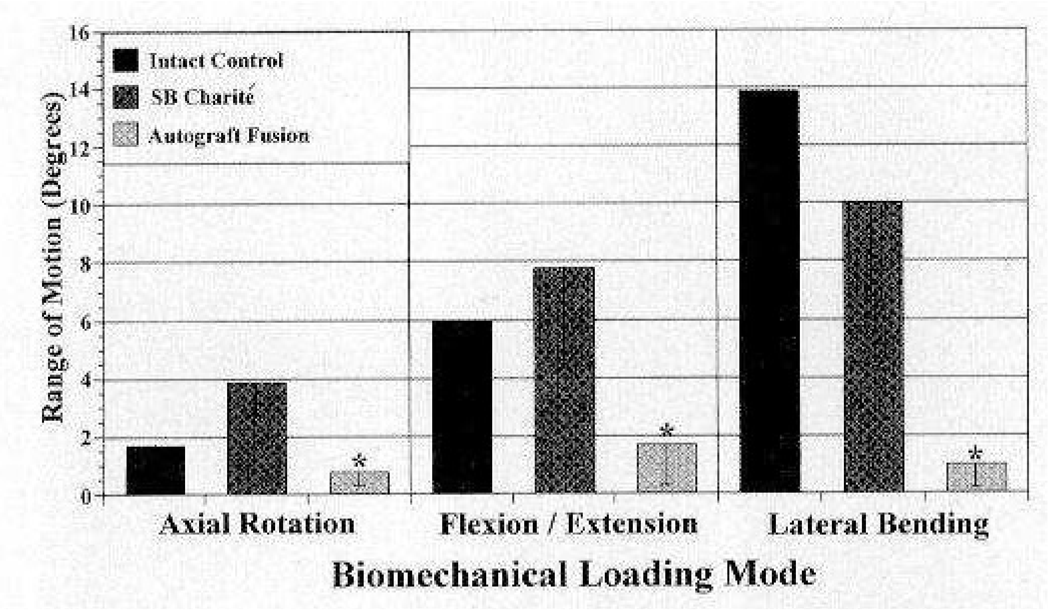


Figure 10

As can be seen in Figure 10 above, the peak range of motion was similar for units which contained the Charité discs and the non-implanted controls. Gross histopathology showed excellent bone ingrowth into the fixation surface with no intervening fibrous tissue. There was no evidence of any significant histopathological changes and the trabecular bone growing directly on the implant surface appeared normal and lamellar (Figure 11). There was no evidence of a peri-prosthetic membrane and the devices appeared well fixed and solidly in-grown. Debris along the end-plate was occasionally observed but this was thought to be an artefact of the histological section preparation rather than derived from a clinical effect.

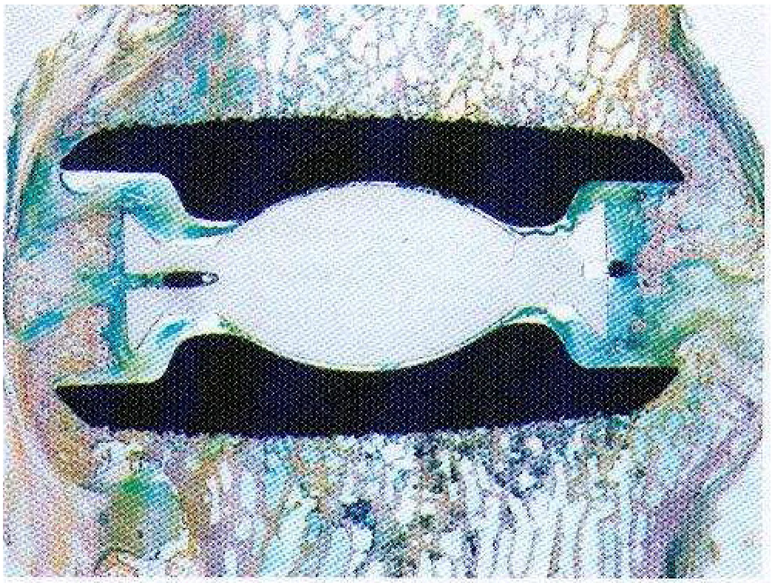


Figure 7. A coronal histologic section of the SB Charité prosthesis. Excellent ingrowth is seen between the hydroxyapatite-coated endplates and the L5 and L6 vertebral bodies 6 months after surgery.

Figure 11

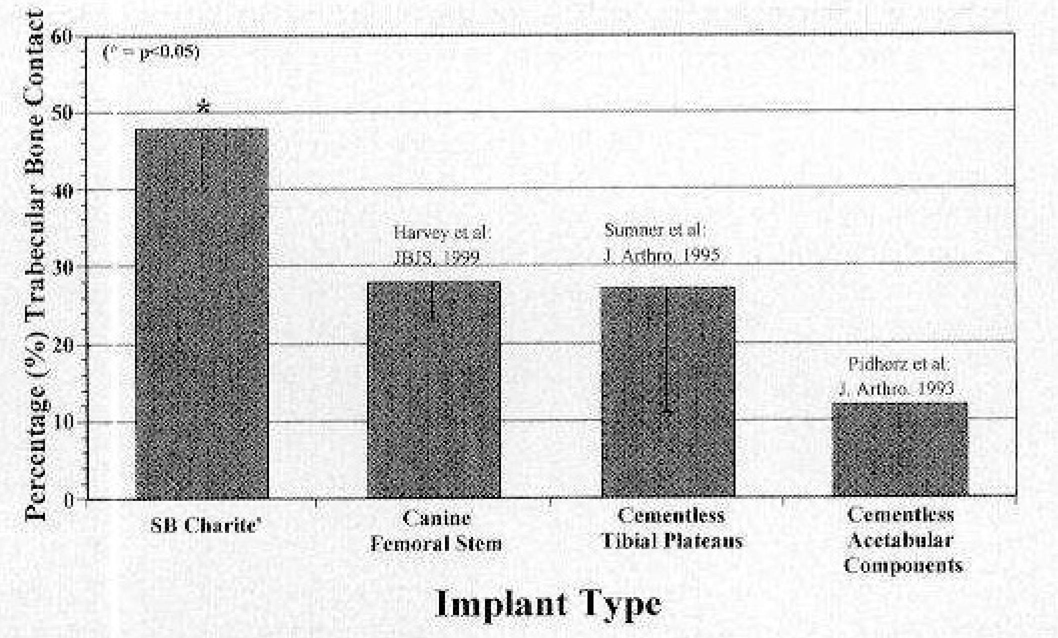


Figure 11. Bar graph illustrates the percentage of ingrowth–bone contact on the endplate surface. Left bar, SB Charité and vertebral body interface. The porous ingrowth for the SB Charité was as favorable as any previously reported for total joint prostheses in the peripheral skeleton.

Figure 12

The mean bone ingrowth was measured for the explant sections (n=4) (see Figure 12 above) and was found to be 47.9 +/- 8.12% (range 35.5 – 58.8%). As it can be seen, this is significantly higher to that previously reported for other animal and human explant studies of ingrowth on recovered hip and knee surfaces. Jasty et al [28]reported bone ongrowth of 28.1 +/- 5.31% for a titanium dog femoral component. 27.1% +/- 16.1% was reported for a human tibial plateau[29]. It was speculated that higher ingrowth in spinal model was due to the sustained compressive loading found across vertebral endplates due to action of the ligaments compared to the intermittent tensile and compressive loading for a femur or tibial plateau.

Canine[30]

Ten hydroxyapatite macroporous surface cups v eighteen BONIT coated macroporous cups were tested. The dogs were sacrificed at six months and histology was performed at four different zones; all the bone/implant surfaces showed increased bone density at zone 2. There was no significant difference observed between the different surfaces but firm osteointegration was found in all cases as shown in Figure 13. (Two were lost from the study due to infection)

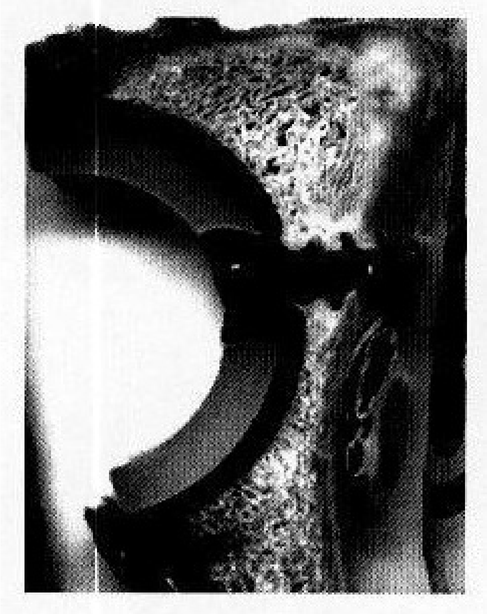


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Figure 13

Another canine study reviewed the effect of immediate loading after implantation. Histological analysis showed that low bone density and poor primary stability reduce effective osseointegration.[31] A further canine study was also performed to investigate the effect of implant micromotion. This test used pins of dimensions 8x 4.1 mm x 6 mm; 4 control samples (plasma sprayed titanium plus plasma hydroxyapatite (HA) surface and 4 test samples (plasma sprayed titanium plus BONIT) were implanted. One HA implant loosened. Bone apposition was measured and it was found that whilst the control showed 56.4+/- 10.6 % bone ongrowth, the BONIT test implant produced 61.0 +/- 26.4 % new bone apposition. In addition, it was seen that the plasma HA had fragmented and particles could be seen embedded in the newly grown bone.

Sheep [32]

Eight dumb-bell shaped implants of titanium-aluminium-vanadium alloy (Figure 14) with end plates, 7mm and mid-section 5mm diameter, with a titanium plasma sprayed 400 micron coating, were implanted into sheep femoral condyles. The study used two uncoated controls, two implants with plasma spray titanium plus a 20 micron BONIT layer and four implants with a plasma spray titanium coating plus 1 micro-gram bone morphogenic protein, rhBMP, injected into the mid-section interfacial 1 mm gap between the implant and bone. The sheep were sacrificed at four and nine weeks. 50% peripheral new bone was found around the BMP enhanced implants (n=2) after four weeks and almost complete ossification of the interface after nine weeks (n=2). No new bone formation was observed around the uncoated titanium or plasma sprayed titanium controls at the same time points. A thin mineralised layer was seen around the BONIT coated implants after nine weeks but not as dense or as extensive as observed with the BMP 2. Podeus osseous beams (Figure 14) were seen extended and bridging the gap between the implant and bone

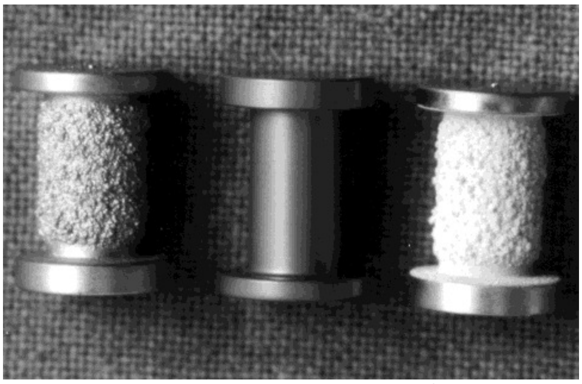

Fig. 1. Dumb-bell shaped implant made from Ti-6Al-4V. Diameter of end-plates: 7 mm; diameter of intermediate test-zone: 5 mm. Left: with titanium-plasmaspray surfacing (TPS). Middle: without TPS (basic design). Right: with calcium phosphate surfacing (CaP) and TPS

Figure 14

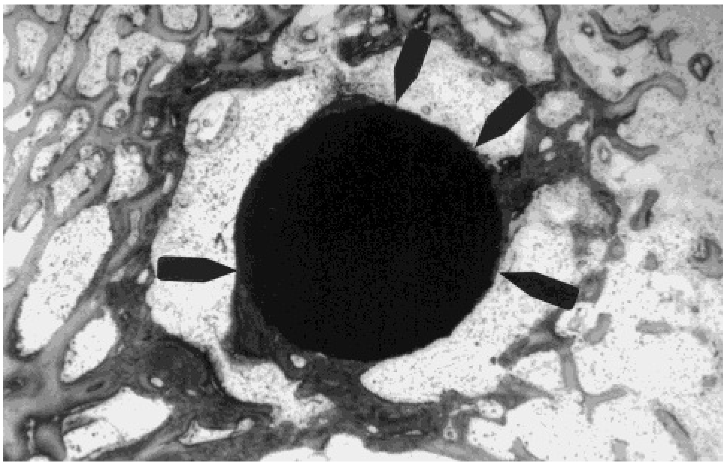

Figure 15

Implant with TPS and calcium phosphate surfacing. Osseous beams bridging the spacious gap. Very thin osseous layer(arrows) enclosing nearly the whole implant (optical microscopy, 9 weeks post surgery, diameter of the implant: 5 mm)

## Rabbit

This study[33] involved a comparison of Ti6Al4V screw shaped implants with and without a 15±5 micron BONIT coating in rabbit tibae and femurs after 6 and 12 weeks implantation. The mechanical removal torque test showed significantly increased values for the coated implants after 12 weeks ($p<0.05$) but not after 6 weeks. Higher bone-implant contact was found for the coated implants in the tibia after 6 weeks and for both tibial and femoral screws after 12 weeks ($p<0.05$). There was no difference in the inflammatory reaction around the implants, and although possible particles of the coating could be detected after 6 weeks, they were not observed after 12 weeks implantation.

## 4. Regulatory and Clinical Results

Since BONIT was first launched in1995, more than 500,000 orthopaedic and dental implants have been coated with BONIT coatings. BONIT has CE approval on many European devices. In addition, several PMA approvals exist for spine studies in the US e.g. P040006 S002, K043079 and K060437). There are various trdae names for different names for BONIT coating e.g.TiCaP (Link) µ-CaP (Aesculap), Protebone (Mathys) and FBR (Oraltronics). Some of these implants have been followed in prospective studies to understand the fixation potential of BONIT compared to other surfaces. These reports are summarised below.

Figure 16 Femoral stems coated with BONIT

### a. Dental

A study [3, 34] of human biopsy samples was made around three coated TPS PITT-EASY dental implants (Oraltronics, Bremen, Germany) after 6, 10 and 12 weeks. All implants fully osseointegrated, with bone ingrowth of 54.4 - 70.1%. The coating disappeared by 12 weeks in vivo.

A further study[35], of 159 PITT-EASY implants, recovered from 56 patients who were restored at 7 and 12 weeks. The cumulative success rate at 30 months was 98.1. A similar study of the coating on 156 ILI implants in 55 patients showed cumulative success of 94.9% at 24 months.[36] Tissue from 3 of the patients from the study underwent histological examination; all implants were fully osseointegrated, Bone ingrowth (BIC) varied from 54.4 - 70.1%. Some coating remnants were found, confirmed that the coating fully resorbs and osseointegrates within a window of 6-12 weeks. A later 2 year review of the 55 patients suggested that failures due to the immediate loading protocol used in the study will not occur after 3-6 months[37] . After a further healing study of the healing rate of these patients it was suggested by the authors that healing times could be halved using BONIT coated implants[38]. Six (6) patients received 22 implants in order[39] to evaluate clinical osteointegration. A reverse torque of 30Ncm was applied to remove the recovered implants from surrounding bone. All the implants successfully resisted this load, suggesting it may be possible to reduce healing time to 4-6 weeks from the current practice of waiting for 6-8 weeks

It is important to note that in all these studies no activated macrophages or giant cells were found at any time point around these explants. This is in contrast to reports of inflammatory cell activity seen around resorbing plasma sprayed HA coatings where occasionally particles can be found undergoing phagocytosis[40] This can be possibly explained by the different dissolution pathways for these solution deposited coatings compared to that for plasma sprayed coatings (see Section 2)

The correlation of all the data from the pig and clinical dental studies[41] was later reviewed. It was concluded by the authors that all the in vivo safety tests for BONIT showed excellent results and that the in vivo efficacy showed statistically significant better osteointegration for the BONIT versus the control after 6 weeks; with direct bone apposition measurements of 73.0+/-6.2% for BONIT versus 49.8+/-16.4% for the control group. This useful review also discussed the existing approaches to coating device and the differences between electro-deposited and plasma sprayed coatings (highlighting the lack of inflammatory responses found with the BONIT coatings) The author discusses the mechanisms associated with the dissolution of BONIT coatings and emphases its resistance to shear or insertion forces (11 to 25.3 MPa was measured in a pull-out test). The BONIT coatings' high surface area, which facilitates good physiological interaction (via a capillary effect), with was thought to be important in its mechanism of action. All the data reviewed by the author suggested that these bioactive coatings do not have to remain long term once osteointegration is achieved. They concluded that the excellent in vivo and clinical dental data can be extrapolated and should predict good results achievable from BONIT coatings on orthopaedic implants.

b. Knee

Reports of the use of BONIT in knee joint fixation can also be found in the literature.361 consecutive unicondylar arthroplasties, using a mobile bearing knee (AMC) (Figure 17) were performed between 1991-2000 [42] [43] The AMC-UC has a fixation surface coated with BONIT. The patient pre-diagnoses included osteoarthritis in 90% and osteo-necrosis in 6% of cases. Four (4) percent had posttraumatic disease after a tibial plateau fracture. The mean age of the patients at the time of the procedures was 69.5 (range: 46.3–88.6) years, and the mean weight 81.3 kg (range: 51.2–128.8). The mean duration of follow-up was 5.5 (2.3–12.5) years. At the time to follow-up 18 patients had died and 6 patients had been lost to follow-up. In a further study, cemented AMC knee replacements were implanted in two hundred and sixty (260) patients, and cementless replacements in eighty nine (89). Twelve (12) knees were hybrids. Three hundred and fifteen (315) procedures involved the medial compartment and forty six (46) the lateral compartment.

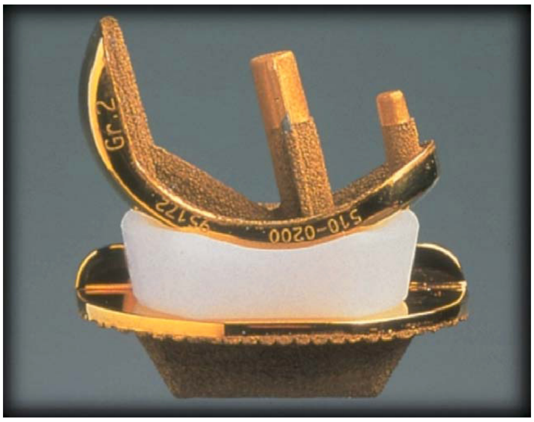

Figure 17

Ninety two percent had a good or excellent clinical outcome. Three knees were revised for mobile bearing dislocation after medial UCA and three for lateral mobile bearing dislocation after lateral UCA. Five revisions were necessitated by component loosening and there was one case of deep infection. The clinical results of the investigated patients demonstrate that the AMC-UCA is a successful concept with safe fixation of the prosthesis. This is a demonstration of the stable interface provided by the BONIT coating on a knee in humans but there was no specific investigation into the properties of the coating. However, the cementless component anchorage of the AMC-UCA was reliable. The tibial cementless plateau failed only in one case, a 46-year-old man. This patient had undergone surgery on the knee five times prior to UCA implantation. Revision was performed successfully using a cemented tibial plateau.  One of the coated tibial components was recovered three months after implantation (tibial condyle fracture with displacement had necessitated the revision). The histology of this explant showed direct apposition of bone to the implant surface. (Figure 18)

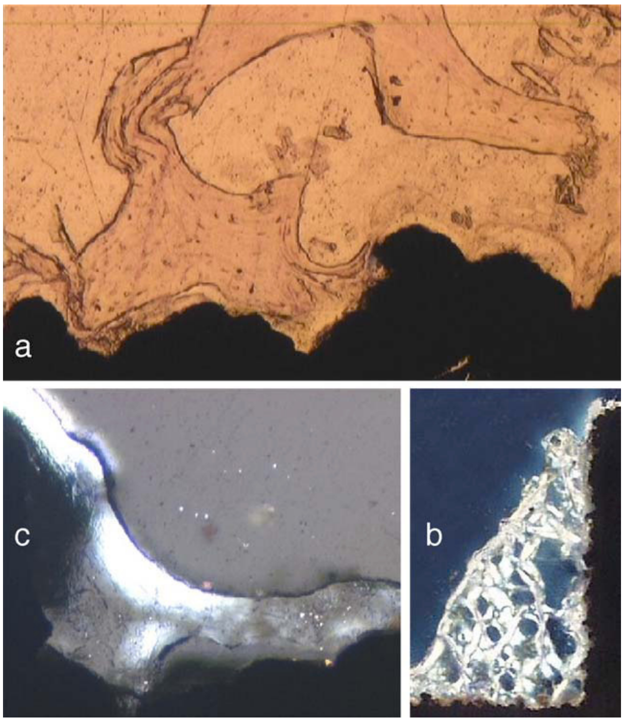

Figure 18 Bone in direct contact to metal surface. (a) Undecalcified, unstained grinding section surface and translucent illumination. (b) Detailed view in polarized light. (c) Overview in polarized light.

### c. Ankle[44]

200 mobile bearing STAR ankle replacements were implanted between 1993 and 2000 with a mean follow up of 46 months. 92.7 % survived at 5 years. 141 radiographs immediately post-op and at 2 years of the patients with surviving ankles were studied. 104 had plasma HA coatings (Osprovit) and 37 had BONIT coated onto plasma sprayed titanium. A radiographic examination immediately post-op. of 47 ankles, showed small gaps at the tibial implant-bone interface, adjacent to the fixation bars. At 2 years a

radiographic follow up of 141 patients indicated that the most important factor governing the appearance was the coating and the pre-existing bone/implant gap. The authors defined appearances as Type A with bone of constant density along the implant surface; and Type B with a line of sclerosis proximal to the implant surface (see Figure 19)

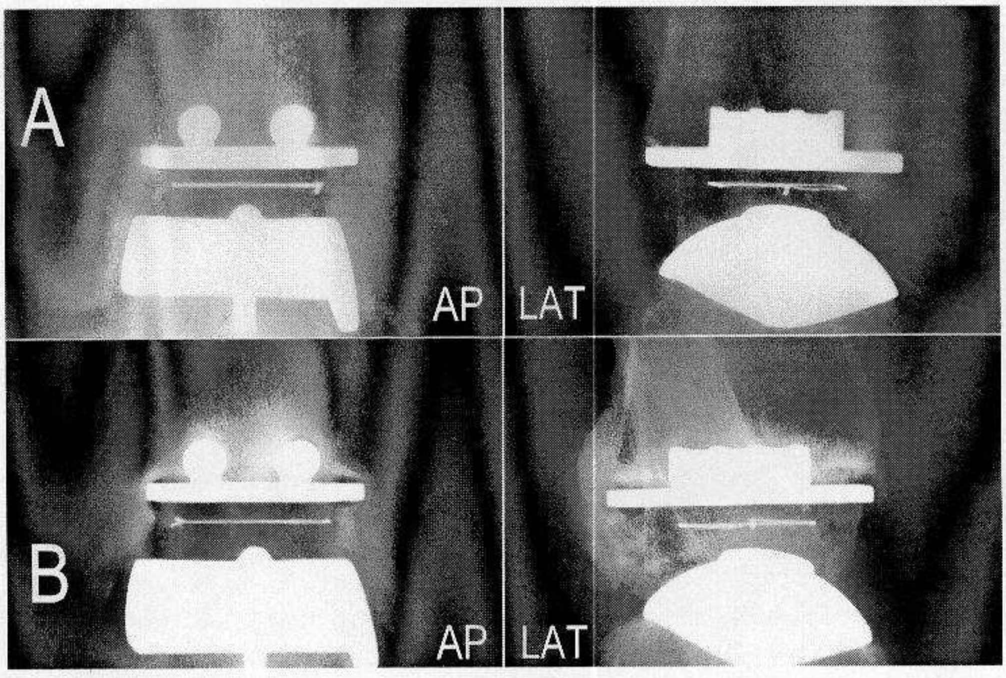

Fig. 6

Radiographs at two years of patients with a good outcome showing the appearances A and B.

Figure 19.

The results fell into two groups (A and B). Type B was seen with those with pre-existing gaps (84%) and with plasma sprayed HA coating (16%). Coating with BONIT were more likely to show the Type A appearance than those with plasma deposited HA surfaces or with pre-existing gaps.

d. Cervical Disc

A study[45] of 53 patients receiving 82 PCM cervical disk arthroplasties with a BONIT-like coating (with a trade name TiCaP in Canada) showed a significant improvement in all scales measured (visual analogue/neck disability index/treatment intensity gradient). 80% of patients had a good or excellent result at 1 week, improving to 90% at 1 month and remaining at 90% at 3 months[46]

# 5 Conclusions and Summary

Animal studies and clinical trials have provided impressive proof of the efficacy of BONIT coatings. Accelerated implant healing, increased bone formation and improved mechanical implant anchoring have been observed especially in the early post-implant phases. This means that the load bearing properties of the implant are robust at an early stage BONIT® coatings are completely resorbed in a controlled way (approximately six to twelve weeks following implantation) and are simultaneously replaced by bone. The coatings are well tolerated and no inflammatory or rejection processes have been reported.

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