Bilayered calcium phosphate coating to promote osseointegration of a femoral stem prosthesis

E. GOYENVALLE[1,2*], N. J. M. GUYEN[3], E. AGUADO[1,2], N. PASSUTI[4], G. DACULSI[1]
[1]*Center de Recherche sur les Matériaux D'Intérêt Biologique, Equipe mixte INSERM 99-03, Faculté de Chirurgie Dentaire, BP 84215, 44042 Nantes Cedex 1, France*
[2]*Service de Pathologie Chirurgicale, Ecole Nationale Vétérinaire de Nantes Route de Gachet, BP 40706, 44307 Nantes Cedex 3, France*
[3]*Laboratoire de Statistique et d'Informatique Médicales, Faculté de Médecine de Nantes, 1 rue Gaston Veil, 44035 Nantes Cedex 01, France*
[4]*Pôle ostéoarticulaire, CHU Nantes, Place Alexis Ricordeau, BP 1005, 44035 Nantes Cedex 01, France*
E-mail: goyenvalle@vet-nantes.fr

A bilayered bioactive-gradient coating, consisting of a superficial layer of biphasic calcium phosphate (BCP) and a deep layer of hydroxyapatite (HA), promotes faster osseointegration and higher shear strength in non-loading conditions than do monolayer BCP or HA coatings. This study evaluated the biofunctionality of this coating in weight-bearing conditions at 6 and 12 months. The coating was plasma-sprayed on the metaphyseal portion of a sandblasted Ti6Al4V canine femoral prosthesis implanted using the surgical press-fit technique. An identical uncoated stem served as the control. Metaphyseal bone-to-implant apposition was increased for coated ($\sim$ 90% and 80% respectively at 6 and 12 months) as compared to uncoated implant ($\sim$ 7% at 6 and 12 months). Limited bone apposition was observed at the diaphyseal level. After 12 months, the uncoated implant interface consisted of well-organized, active fibrous tissue, whereas only inactive fibrous tissue interposition was observed at diaphyseal levels of the coated implant. At 6 months, the mineralization apposition rate (MAR) was similar, regardless of implant or bone structures. At 12 months, a significant decrease of MAR was observed around the uncoated implant. Transmission electron microscopy studies of the interface showed precipitation of biological apatite crystals in close association with mineralized collagenous bone matrix. Our results suggest a direct relationship between bioactivity and enhanced bone formation. The sandwich coating used is effective in promoting massive metaphyseal osseointegration, which ensures mechanical stability for early weight-bearing and should prevent long-term complications.

Introduction

Articular prosthesis surgery should ensure early fixation of inert materials to living bone as well as the long-term stability of the implant. Numerous systems have been developed to obtain implant fixation, such as mechanical and cemented or porous cementless fixation. However, all have shown limitations concerning the long-term stability of the implant [1–3]. The main problem with cementless fixation is limited bone apposition at the implant surface, as most of the interface consists of fibrous tissue with poor mechanical properties [1, 2, 4–6]. Thus, the concept of bioactive fixation has been developed in recent years to promote bone apposition and ensure long-term implant stability. This approach, which is based on the use of bioactive materials such as calcium-phosphate ceramics, has provided good clinical results [3, 7–13]. Calcium-phosphate coating has certain advantages for implantation, including a composition close to that of the bone mineral matrix [14], biocompatibility [14], and bioactivity [15–17]. After the resorption/bone substitution process, plasma-sprayed calcium-phosphate coating can promote and enhance bone apposition at the surface of a metallic implant [4, 6, 13, 18–26]. The optimal characteristics of bioactive coating ceramics are those that enhance osseointegration of the metallic implant as early as possible during the postoperative period and maintain lasting bone apposition. These factors are essential for the short- and long-term stability of the implant. The bioactivity of calcium-phosphate ceramics is correlated with their solubility [14–16, 23] and depends particularly on their physicochemical characteristics [14, 17, 23]. In non-loading conditions in

*Author to whom all correspondence should be addressed.

rabbits, Delecrin *et al*. [27] showed that a biphasic calcium-phoshate (BCP) coating containing 60% hydroxyapatite (HA) and 40% β-tricalcium phosphate (TCP) before plasma spraying allowed faster formation of lamellar haversian bone than HA alone. Moreover, a composite coating consisting of a superficial layer of BCP and a deeper layer of HA ceramic (a sandwich coating) exhibited the highest shear strength as compared to BCP or HA coating alone, which suggests that there is a direct relationship between bioactivity and enhanced bone formation. Our objectives were to study the histological and ultrastructural interfaces obtained with this solubility-gradient sandwich coating in biological conditions close to those encountered with human femoral hip prostheses and to evaluate its long-term biofunctionality as a metaphyseal coating for the femoral stem.

Materials and methods

Implant model

A femoral stem prosthesis was designed specifically for female beagles. Two types of implants with identical geometry were used: a partially metaphyseal sandwich-coated implant and an uncoated implant that served as a control (Fig. 1). Both implants were made of titanium alloy (Ti6Al4V), and the surface was treated by sandblasting and passivation. The sandwich-coating procedure consisted of an initial 20-μm-thick plasma spray of HA, followed by a 30-μm-thick plasma spray of BCP (60% HA and 40% β-TCP; Zimmer, France). The characteristics of the starting powders and ceramic coatings, including analysis of transformations after plasma-spraying, adherence and roughness analysis, were described previously [27, 28]. After the plasma-spraying procedure for HA and BCP, the respective contents were 85–90% HA plus an α-TCP content of 10–20% under amorphous phases and 55% HA and 45% α-TCP, with amorphous phases accounting for around 30–35% BCP. Coating adherence was 5 ± 0.87 Mpa.

Animal model

Six female beagles, 3–8 years of age and weighing 10–14 kg, were operated bilaterally. A coated femoral stem was implanted first on the left femur, using the press-fit technique with an undersized reamer. Four weeks later, the uncoated implant (control) was impacted similarly on the right femur. During the first 14 postoperative days, the operated limb was placed in a non-weight-bearing position, using an Ehmer sling to prevent hip luxation secondary to rupture of the articular capsule suture. After this period of restricted activity, the dogs were allowed full weight-bearing. Functional recovery was evaluated according to the rating system of Gendreau and Cawley [29]. Radiographs were performed postoperatively at half implantation time and immediately after euthanasia. For double bone labeling, an intramuscular injection of 0.2 ml/kg of oxytetracycline (Terramycine©, Pfizer) was performed at day -20, -19 and -8 to -5 before euthanasia (day 0). After 6 and 12 months respectively, two and four dogs were euthanized under general anesthesia by perfusion of a 5% formaldehyde solution. The implantation intervals were calculated from the implantation time for the coated implant. All animals used in this study were bred for scientific purposes. Their care and use were in accordance with French law on animal experimentation.

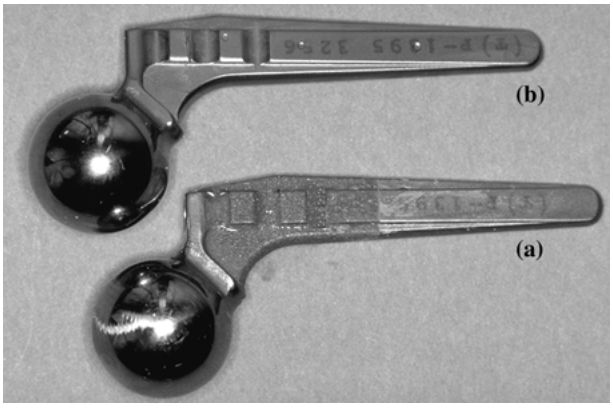

Figure 1 The two types of implants: (a) Metaphyseal sandwich coated implant, (b) Uncoated implant.

Histological analysis

For histological fixation, femurs were immersed in a glutaraldehyde/formaldehyde solution buffered at pH 7.2 by a sodium cacodylate solution.

For each femur, four section levels (A1, A2, A3, A4) were defined, as shown in Fig. 2. At each level, two 6-mm-thick samples were obtained, one for calcified (C) and the other for decalcified (D) tissue analysis. Levels A1C, A1D and A2C concerned the coating area. Calcified tissue samples were embedded in methyl-methacrylate and then cut with a diamond saw (Isomet 1180 low-speed saw, Buehler, USA) into 100-μm thick sections that were microradiographed at 15 kV and 25 mA for 30 min. For decalcified tissue preparation, the titanium implant was extracted by immersion in nitrous liquid. Bone samples were decalcified by immersion in a solution containing 10% formaldehyde RP solution, 5% nitric acid RP and 85% distilled water. Decalcified tissues were then embedded in paraffin blocks, cut with a microtome (Supercut 2050, Reichert-Jung, RFA) into 7-μm thick sections and stained with

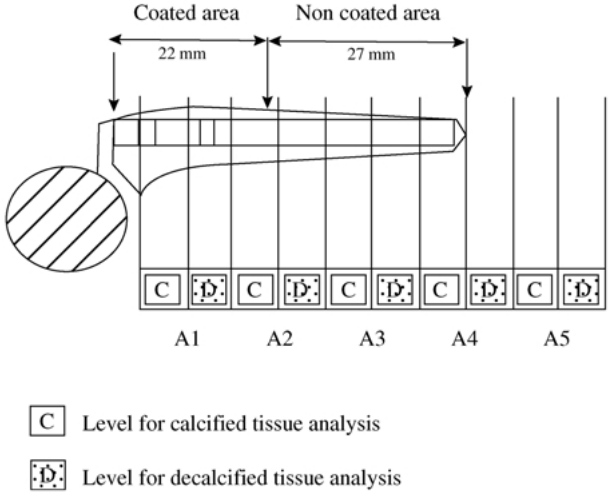

Figure 2 Different levels of the femoral stem section.

Masson's trichrome. Qualitative analysis of the interface was performed in light microscopy and backscattered electron microscopy (BSE) (6300, Jeol, Japan). At each level of the calcified samples, the percent of bone-to-implant apposition (BIA) and the percent of fibrous tissue distribution (FTD) were evaluated by a linear intercept technique and by line-counting [30]. BIA and FTD were defined respectively as bone and non-mineralized well-organized collagenic tissue in direct contact with the calcium-phosphate coating or the metallic substrata. To cover the entire periphery of the implant, BIA and FTD were calculated in adjacent successive fields by light microscopy observation ($\times$ 220) of microradiographs and sections under polarized light. All measurements were done in triplicate at one-week intervals to control the reproducibility of the method and to minimize operator variations. For each sample, BIA and FTD were defined as the mean of the three measurements. Tetracycline double bone labeling was observed under fluorescent light at magnification $\times$ 250, as recommended by Frost [31]. Three area were chosen at coating levels A1 and A2: the interface with the implant, trabecular bone and cortical bone. Results for the mineral apposition rate (MAR) are expressed in µm/day.

Ultrastructural analysis

Samples were obtained from 100-µm thick calcified sections of both implants in areas that seemed of interest in light microscopy analysis. The technique of Linder *et al*. [32] was used to preserve the bone-coating interface without titanium. These samples were embedded in methyl-butyl-metacrylate and cut with a diamond knife (Ultracut E, Reichert-Jung) into ultrathin sections (80–100 nm thick). They were contrasted with uranyl acetate and lead citrate and then observed in transmission electron microscopy (Jeol TEMSCAN 200 CX).

Statistical analysis

Each subject was observed several times under different conditions. This linear model with repeated measurements was then assessed using BMDP 5V software (BMDP 7.0, University of California Press, Berkeley, CA, USA). Friedman and Mann-Whitney tests were used in each group when interactions between variables were significant. A working significance level of 0.05 against the one-sided alternative was required.

Results

Clinical evaluation

Full weight-bearing on operated limbs was observed two weeks after withdrawal of the Ehmer sling. No difference in functional recovery was noted between coated and uncoated implants (Chart 1). No infectious or functional complications were observed during the implantation period. Radiographic analysis showed differences at the host bone-femoral stem interface in both implants. Regardless of the implantation interval for the coated implant (6 or 12 months), intimate radiological bone contact was apparent in the metaphyseal part of the stem opposite the coating. Distally, in the uncoated part, a translucent line parallel to the implant was noted at the interface (Fig. 3). A similar translucent line was present over the entire surface of the uncoated implant, regardless of the interval (6 or 12 months) (Fig. 4).

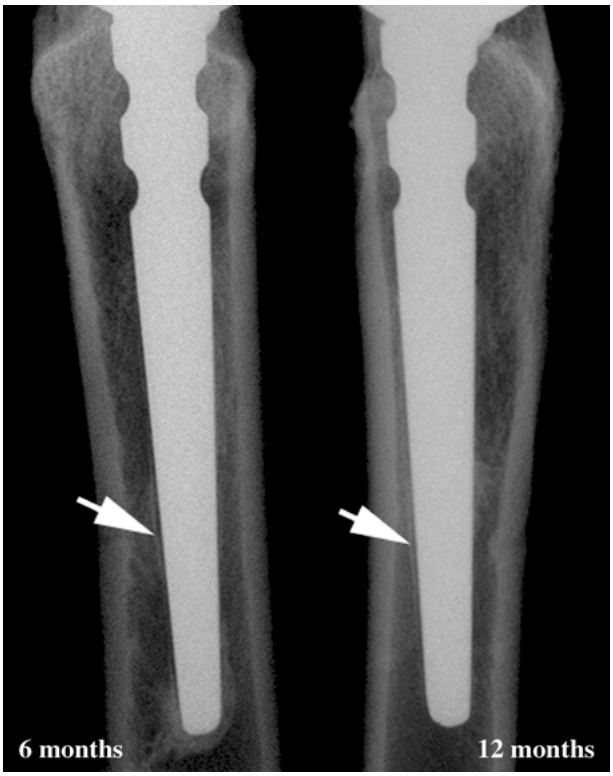

Figure 3 Post-mortem radiographs (lateral view) of the sandwich-coated implant after 6 and 12 months of implantation. Arrows indicate the presence of a translucent line around the distal uncoated part of the stem.

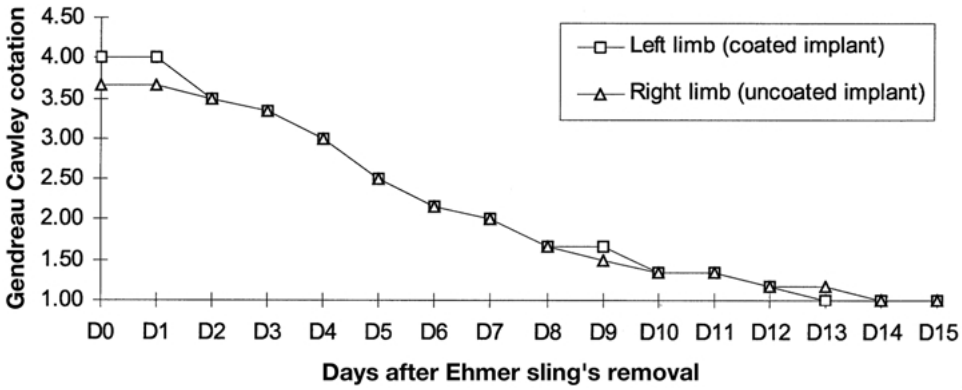

Chart 1 Evolution of functional recuperation, according to Gendreau–Cawley quotation [29].

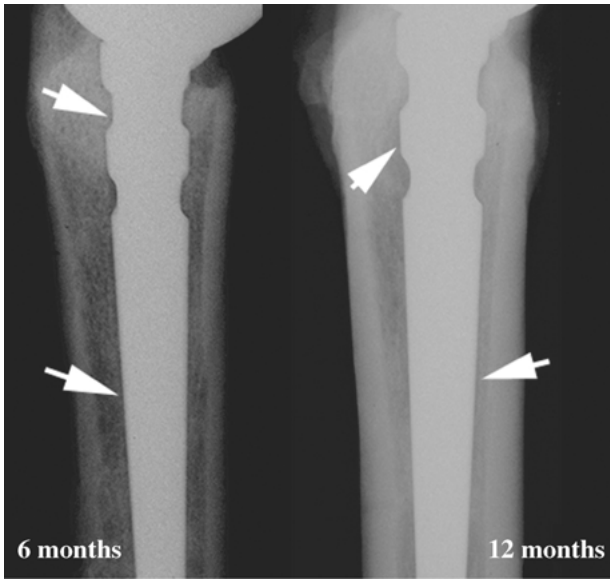

Figure 4 Post-mortem radiographs (lateral view) of the uncoated implant after 6 and 12 months of implantation. Arrows indicate the presence of a translucent line all around the stem.

Histological analysis

At A1 and A2 levels, fine trabecular bone was in close contact with the *coated implant* and seemed to spread out at its surface, with no fibrous interposition (Figs. 5(a) and 6(a)). Distally, bone apposition was more limited on the coated implant (levels A3 and A4) (Fig. 7). The translucent spaces observed on microradiographs were identified on decalcified sections as fibrous tissue composed of a loose network of parallel fibroblast-poor collagen fibers. Bone apposition was poor around the *uncoated implant*, regardless of section level (Figs. 5(b) and 6(b)). At metaphyseal levels (A1 and A2), the density of bone trabeculae increased after 6 months of implantation (Fig. 5(b)) as compared to the coated implant (Fig. 5(a)). Most of the interface was composed of fibrous tissue rich in cells and blood vessels (Fig. 8(a)), together with fibrocartilaginous cells in a few areas (Fig. 8(b)).

Histomorphometrical analysis

Bone-to-implant apposition (Table I, Charts 2 and 3)

At A1–A2 levels, BIA was significantly increased for the coated as compared to the uncoated implant, with no differences between 6 and 12 months for either implant. Distally (levels A3–A4), BIA was limited for both implants, regardless of implantation interval, and decreased significantly between 6 and 12 months. For the coated implant, osseointegration was greater proximally at the coating level (A1–A2), whereas osseointegration of the uncoated stem occurred preferentially around distal levels (A3–A4), particularly at 6 months.

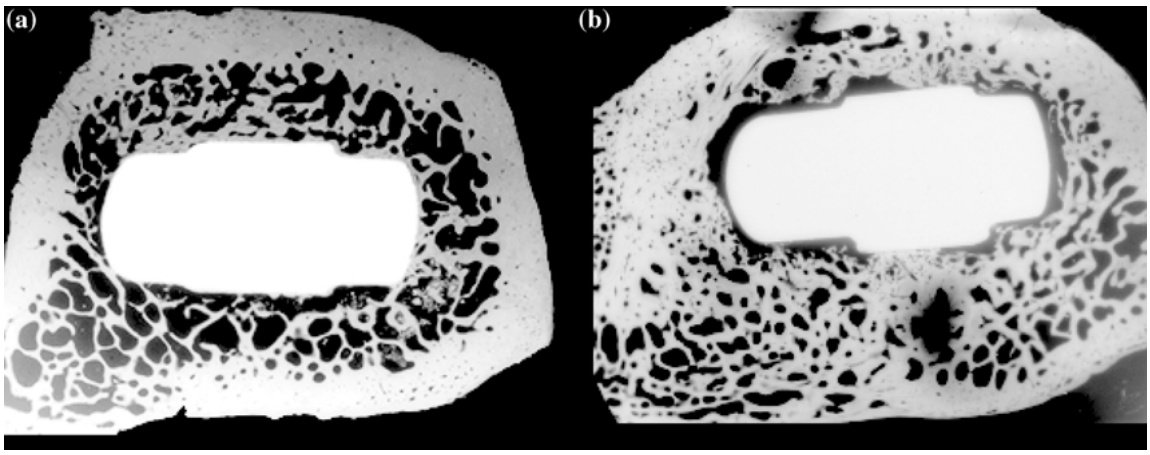

Figure 5 Contact microradiography (6 months) at A1 level for sandwich-coated (a) and uncoated (b) implants.

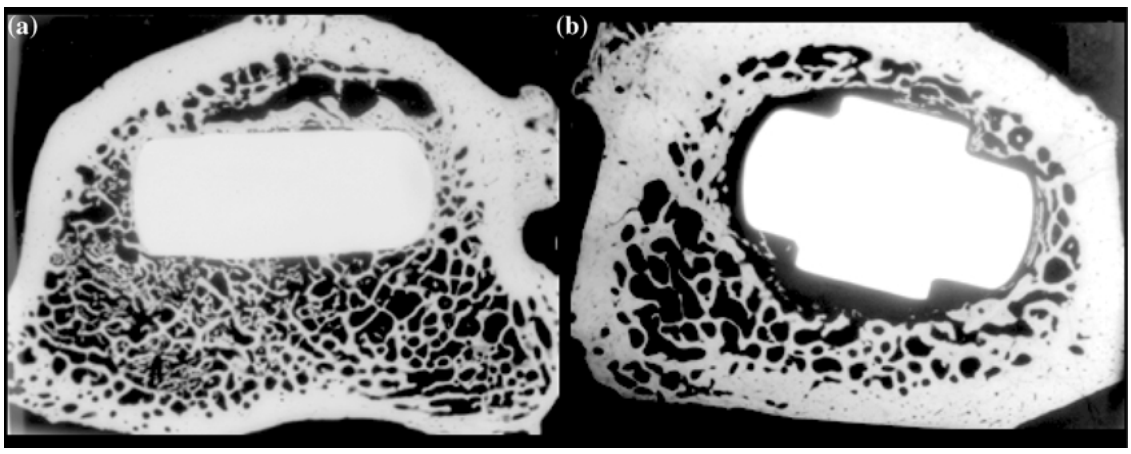

Figure 6 Contact microradiography (12 months) at A1 level for sandwich-coated (a) and uncoated (b) implants.

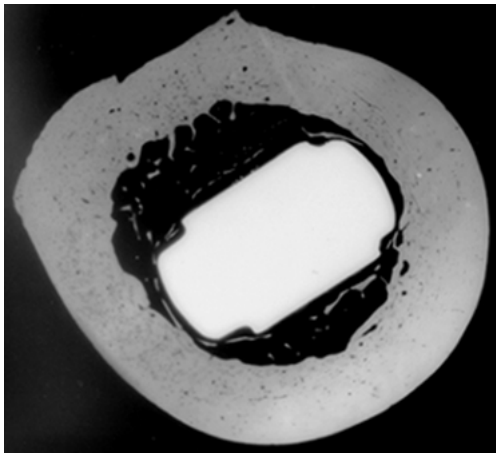

Figure 7 Contact microradiography (12 months) at A3 level for sandwich-coated implant.

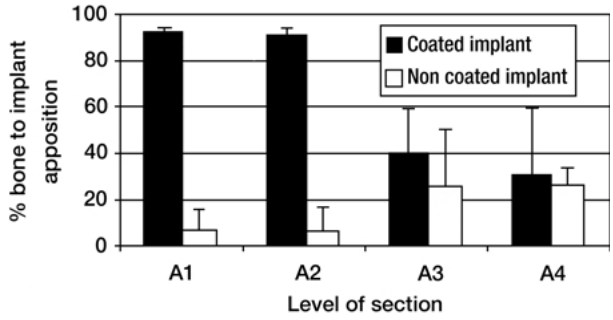

Chart 2 Bone to implant apposition at 6 months, around coated and uncoated implants.

Fibrous tissue distribution (Table II, Charts 4 and 5)

At A1–A2 levels, fibrous tissue was preponderant around the uncoated stem, but almost non-existent around the coated implant, with no apparent differences between 6 and 12 months. At 6 months, more fibrous tissue was observed distally (A3–A4 levels) around uncoated than coated implants. For both implants, a significant increase of fibrous tissue interposition was observed distally between 6 and 12 months, resulting in similar distal FTD after 12 months of implantation. For the coated implant, fibrous tissue was located mainly around the distal portion of the stem, showing a significant increase at 12 months. For uncoated implant, fibrous tissue at 6 and 12 months was distributed uniformly all along the interface.

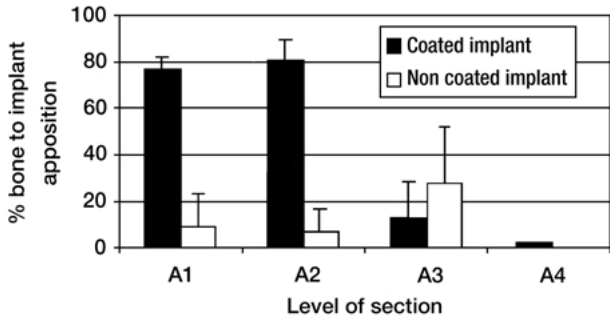

Chart 3 Bone to implant apposition at 12 months, around coated and uncoated implants.

Tetracycline double bone labeling (Charts 6 and 7)

After 6 months of implantation, MAR appeared to be stable for each implant, regardless of site ($p = 0.89$), and for each site, regardless of implant (coated or uncoated) ($p = 0.13$). After 12 of months implantation, MAR remained uniform for the different bone sites of each implant ($p = 0.70$). A significant decrease of MAR was observed for uncoated versus coated implants at each bone site (cortical, trabecular or interface) ($p < 0.05$).

Ultrastructural analysis

The coating appeared to be an association of differently-shaped crystals. The structures observed (Fig. 9) were (1)

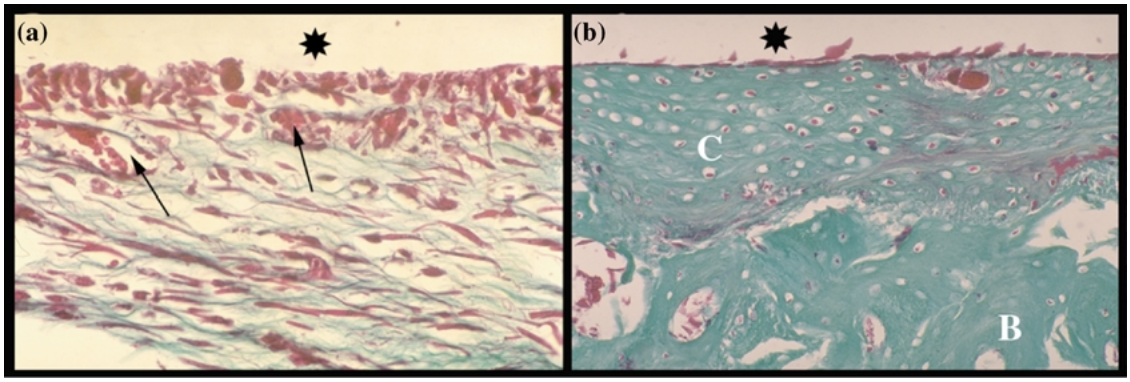

Figure 8 Appearance of fibrous tissue around the uncoated implant – Masson's trichrome (★ indicates the interface with the implant): (a) Fibrous tissue rich in cells and blood vessels (→) – original magnification × 480; (b) Presence of fibrocartilaginous cells (c) at the interface with bone (b) – original magnification × 240.

TABLE I Statistical significance for bone-to-implant apposition: effect of coating, delay and level on the stem

Coated versus uncoated		6 months versus 12 months		A1–A2 versus A3–A4	
A1–A2 (6 months)	< 0.05	Coated (A1–A2)	1	Coated (6 months)	< 0.05
A3–A4 (6 months)	0.81	Uncoated (A1–A2)	1	Uncoated (6 months)	< 0.05
A1–A2 (12 months)	< 0.05	Coated (A3–A4)	< 0.05	Coated (12 months)	< 0.05
A3–A4 (12 months)	0.165	Uncoated (A3–A4)	< 0.05	Uncoated (12 months)	0.54

TABLE II Statistical significance for fibrous tissue distribution: effect of coating, delay and level on the stem

Coated versus uncoated		6 months versus 12 months		A1–A2 versus A3–A4	
A1–A2 (6 months)	< 0.05	Coated (A1–A2)	1	Coated (6 months)	0.54
A3–A4 (6 months)	< 0.05	Uncoated (A1–A2)	1	Uncoated (6 months)	0.54
A1–A2 (12 months)	< 0.05	Coated (A3–A4)	< 0.05	Coated (12 months)	< 0.05
A3–A4 (12 months)	0.26	Uncoated (A3–A4)	< 0.05	Uncoated (12 months)	0.21

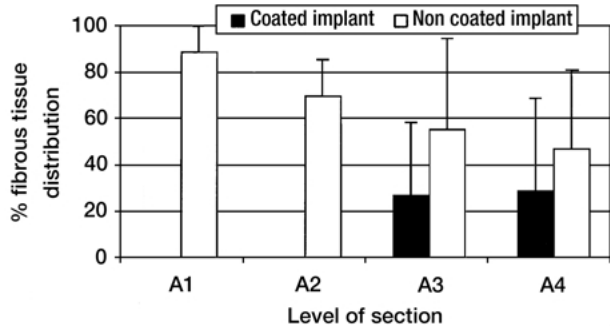

Chart 4 Fibrous tissue distribution at 6 months around coated and uncoated implants.

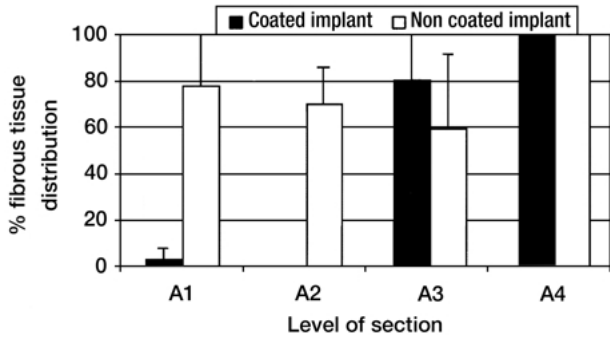

Chart 5 Fibrous tissue distribution at 12 months around coated and uncoated implants.

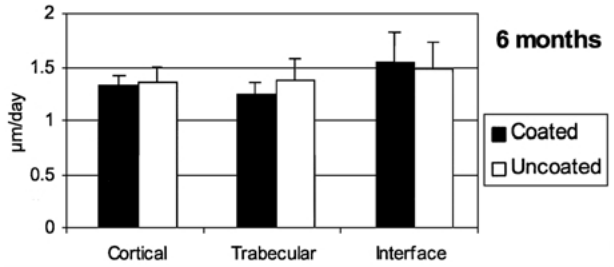

Chart 6 Mineral apposition rate at 6 months, around the metaphyseal part (levels A1–A2) of coated and uncoated stems.

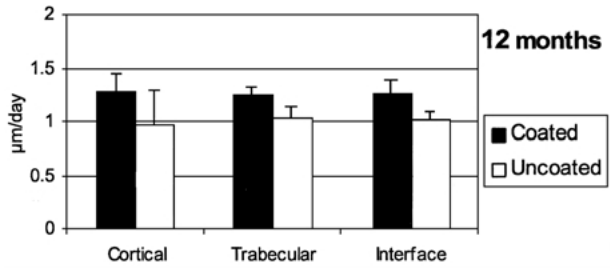

Chart 7 Mineral apposition rate at 12 months, around the metaphyseal part (levels A1–A2) of coated and uncoated stems.

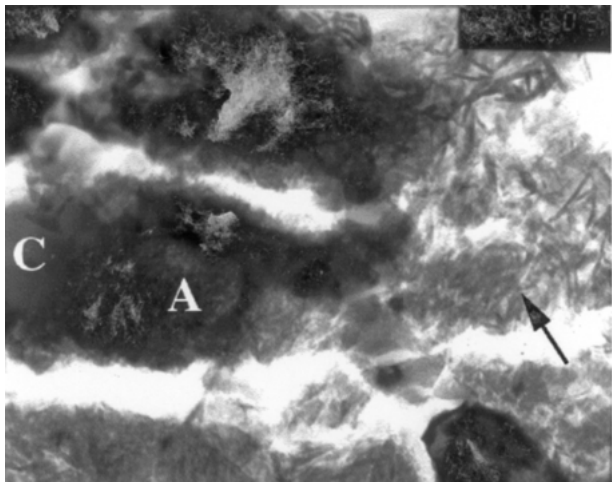

Figure 9 Different crystals observed in the coating: (c) synthesis crystals, (a) apatite reprecipitation process, (arrow) mineralization by epitaxis growth and secondary nucleation (original magnification × 50 000).

large crystals, with smooth or irregular surfaces, corresponding to synthetic crystals; (2) small needle-shaped crystals located perpendicular to the surface of the large crystals and corresponding to the precipitation of biological apatite by the epitaxic growth process and secondary nucleation; and (3) agglomerates of small crystals at the surface of larger ones that were suggestive of the apatite reprecipitation process. Collagen fibers were seen in direct contact with these different crystals and in close association with small needle-shaped crystals characteristic of bone (as confirmed by X-ray microanalysis). This mineralized collagenous matrix invaded the space between large synthetic crystals (Fig. 10), and this matrix appeared to be closely associated with the small precipitated crystals. The fibrous interface around uncoated implants showed no signs of mineralization at the ultrastructural level.

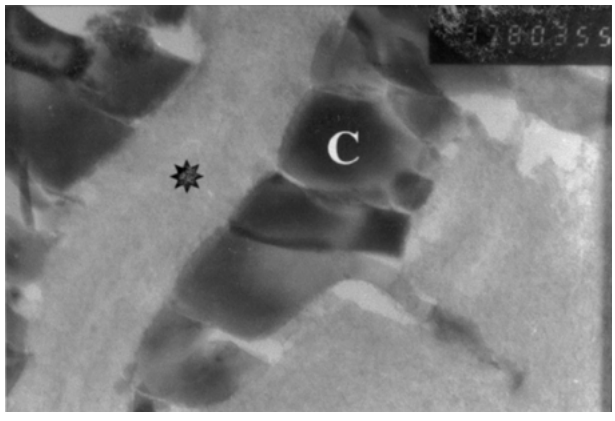

Figure 10 Colonization of spaces between synthetic crystals (c) by a mineralized bone matrix (★) (original magnification × 37 000).

Discussion

The three main findings of this study were as follows: First, plasma-sprayed sandwich coating enhanced and maintained local osseointegration of the partially metaphyseal-coated femoral stem, either by chemical bonding between bone and the coating or direct bone apposition at the surface of the metallic implant. Second, the control femoral stem (uncoated), which had exactly the same shape, geometry, and surface micro- and macrotexture as the sandwich-coated implant, showed obvious signs of loosening as early as 6 months. Third, sandwich coating had no effect on long-term distal FTD, but modified the nature of fibrous tissue, which suggests that different stability conditions existed. The biological integration of a metallic implant into bone involves a balance between osseointegration and fibroosseointegration [14, 23]. Ideally, osseointegration should be reached as early as possible and maintained over time in order to ensure long-term stability of the implant. In the field of uncemented arthroplasty, the parameters allowing short-term fixation may not be the most important ones for long-term stability. The factors acting on early fixation include biocompatibility, primary stability [21, 33], implant surface texture [13, 23] and the use of bioactive coating [8, 13, 18, 19, 23, 24, 33–36]. Factors such as implant geometry and rigidity appear to be more important for long-term fixation [1]. Despite identical biocompatibility, implant design and primary stability (press-fit surgical technique and loading conditions) for both implants, biological integration of the sandwich-coated and control implants showed important differences in terms of bone apposition, fibrous tissue distribution and morphology, and the mineralization rate.

Primary stability effects

Primary stability, defined as mechanical stability in the immediate postoperative period, is considered to be essential for early osseointegration of uncemented implants [21, 23], even when calcium-phosphate coating is used [20, 35, 37, 38]. Primary stability is correlated with implant geometry [39], quality of the surgical press-fit of the implant [20, 21, 26, 35, 40] and loading conditions [41, 42]. Despite the limitation of weight-bearing to 14 days, our results demonstrate that primary stability alone cannot ensure massive osseointegration. The presence of the calcium-phosphate coating appeared to be essential for obtaining bone anchorage of the uncemented stem used, as described in other studies [4, 6, 8], even when the initial fit was poor [21, 24, 26, 33, 38]. In clinical studies [9, 10], HA-coated femoral stems, as compared to uncoated stems, showed lower migration early after surgery, which is a predictive factor for long-term survival of prostheses. Loading conditions have been shown to interact with the bone healing process [38, 42]. Early and massive weight-bearing strains induce micromovements at the interface that may disturb primary stability early after surgery, as shown with porous-coated implants [41, 43]. As observed by us with the control stem, this phenomenon can promote the differentiation and development of interfacial active fibrous tissue [33, 38, 43, 44], involving hypertrophy of adjacent bone [43]. This is considered to be a major source of failure of uncemented implants [23] and might account for the variable limited bone apposition observed with uncoated or porous-coated implants [1, 4]. Our results confirm that the presence of this bilayered calcium-phosphate coating is a protective factor for the initial primary stability of the implant, allowing earlier weight-bearing without precluding osseointegration, as reported for HA coatings [18, 35, 36]. Oonishi *et al*. [25] showed that HA-coated implants can support weight-bearing as early as 2–4 weeks compared to 5–7 weeks for uncoated implants. The biological integration of uncemented implants depends on the slow development of bone-healing mechanisms in the context of an early degradation of primary stability resulting from strains due to weight-bearing. Calcium-phosphate coatings can improve short-term bone apposition [4] because of osteoconductive properties acquired subsequent to a dissolution-precipitation-bone substitution process [17, 22, 34, 45], even when the space between bone and implant is limited [21, 37, 40, 46]. In this context, it would seem preferable to use a calcium-phosphate coating displaying greater bone affinity in order to decrease the period in which initial mechanical stability needs to be maintained.

As demonstrated by ultrastructural analysis (Figs. 8 and 9), the capacity of calcium-phosphate coating to promote osteoconduction at the implant surface depends on a resorption-degradation-bone substitution mechanism responsible for strong bone chemical bonding that is detrimental to the calcium-phosphate coating [4, 5]. This process takes place at the coating surface after the growth of newly formed microcrystals, whose size, shape and structure are similar to those of bone apatite crystals [15, 16, 22, 45]. This phenomenon has been described as osseocoalescence by Daculsi *et al*. [16]. Geesink *et al*. [5] showed that the chemical fixation afforded by an apatite-coated implant provides mechanical strength comparable to that of cortical bone itself. As the optimal characteristics of bioactive coating are those that enhance bone-tissue growth rates at the implant surface immediately after surgery, their bioactivity is correlated with their solubility in contact with biological fluid [14, 15].

Compared to other calcium-phosphate ceramics, such as TCP or BCP, HA has low solubility and reduced bioactivity [14]. However, plasma-sprayed HA ceramics used in an articular prosthesis have slower resorption kinetics than those of more soluble ceramics such as TCP, so that the coating remains for a longer period and provides better long-term osseointegration [24, 46]. According to Maxian *et al*. [24], resorbable HA-coated implants show their greatest interface strength early, whereas bone apposition and attachment strength is lower than that of non-resorbable HA coatings at later time points. As β-TCP is more resorbable than HA *in vivo*, variations in the HA/β-TCP ratio on the plasma-sprayed surface may provide a means of controlling surface dissolution of the coating. Delecrin *et al*. [27] demonstrated that BCP coating in non-loading conditions allowed faster short-term formation of lamellar haversian bone at its expense than did HA, and/or through direct deposition on the ceramic coating surface. This enhanced growth results in greater push-out

strengths when BCP is used as a superficial layer together with a deep layer of HA (sandwich coating). In fact, the bioactivity gradient decreases form the surface toward the depth of the coating. The first layer of BCP allows rapid osseointegration of the implant as early as 3 weeks [27], while the deeper and more stable layer of HA maintains physiologic bone remodeling at the surface of the implant [24]. Although the sandwich coating is superior to HA or BCP alone in non-loading conditions, our study confirms the biofunctionality of this new concept of bilayered calcium phosphate coating in loading conditions similar to those encountered in human surgery, that is, its capacity to promote implant fixation and maintain osseointegration between 6 and 12 months. Although there is controversy concerning the long-term survival of osseointegration around calcium-phosphate coatings [19, 35], the early circumferential bone ingrowth afforded locally by calcium-phosphate coating was found to prevent distal endosteal access to wear debris [11, 47], which has been designated as a main cause of aseptic loosening [2].

Behavior of the uncoated surface

Sandwich coating only ensures local osseointegration of the stem coating level, as in the case of other calcium-phosphate coatings [12, 48]. Despite good metaphyseal osseointegration and achievement of mechanical stability, histological analysis showed that peripheral fibrosis develops around the distal coated stem, as suggested by post-mortem radiographs (Fig. 3). Although post-mortem radiographs (Figs. 3 and 4) showed no differences in the appearance of the radiolucent line surrounding the distal part of both stems, decalcified sections displayed evident differences in the nature of fibrosis. Fibrous tissue around the control implant was more vascular and rich in cells, with numerous fibrocartilagenous cells in a few areas. This thick active fibrous layer around the entire uncoated stem surface was surrounded by active trabecular bone of greater density. These observations are characteristic of the existence of motion between implant and bone [4, 43, 44] and confirm that the control stem was unstable as early as 6 months. For the coated stem, the fibrous layer was only present distally around the smooth part of the stem and showed the characteristics of an inert tissue (a loose network of parallel collagen fibers with few cells). This distal fibrous layer was different from that observed all around the control implant. The lines around the distal portion of the proximally fixed stem suggested relative motion at the interface [49], which is usually attributed to a difference in the modulus of elasticity between implant and adjacent bone [12]. This type of fibrosis does not preclude implant stability and may be indicative of effective proximal stress transfer of mechanical strain, which is an essential factor for long-term survival of the prosthesis, as observed in the clinical situation [12].

Proximal fixation effects

Insertion of an implant into the medullar cavity of the femur may induce modifications in the distribution of bone load [49–52]. Uncemented and porous-coated prostheses can induce proximal cortical and cancellous bone loss, as the load is transmitted from the middle or distal aspects of the stem to the diaphyseal cortex, thereby inducing metaphyseal ''stress shielding'' [3, 50, 52, 53]. In this context, it seems reasonable to use an implant design that allows proximal load transfer, such as a coating confined to the proximal third or half of the implant, which leaves the distal portion of the stem relatively smooth. In terms of this concept, several studies [3, 12, 53, 54] have shown that proximal ingrowth coating on the implant (as opposed to coating of the entire implant) is associated with a remodeling pattern suggestive of transmission of the load to the proximal metaphyseal cortex. Our results indicate that proximal osseointegration around the metaphyseal sandwich-coated implant caused fewer physiological metaphyseal bone disturbances than with uncoated implant. Although metaphyseal bone mass for the coated implant appeared to be qualitatively similar at 6 and 12 months (Figs. 5(a) and 6(a)), it seemed to decrease for the uncoated implant (Figs. 5(b) and 6(b)). These qualitative data were correlated with quantitative MAR results. Independently of bone structure (cortical, trabecular, interface), the bone mineralization rate at 6 months appeared to be stable for both coated and uncoated implants (Chart 6). Conversely, bone mineralization at 12 months decreased significantly around the uncoated implant (Chart 7), indicating a gradual degradation of the mineralization process in the absence of coating. As suggested by Hofmann *et al*. [48], the MAR difference between the two implants should not be related to sandwich coating bioactivity, but to the difference in proximal bone fixation resulting from bioactivity. First, this difference concerned all compartments of proximal bone and was not limited to the interface. Second, the coating had no effect on the mineralization rate, as no MAR difference was observed at 6 months at the interface between coated and uncoated implant. This confirms the results of other studies showing that calcium-phosphate coatings have only a transient effect on the mineralization rate at their surfaces [18, 48]. This indicates that metaphyseal sandwich coating allowed better physiological stress transfer along the metaphyseal shaft of the femur, which is an important factor in the prevention of proximal stress shielding, as demonstrated by the use of DXA techniques in follow-up studies of HA coating [51, 52].

In conclusion, our study demonstrates the biofunctionality of the sandwich coating over a 12-month period in loading conditions similar to those encountered in humans. Our results suggest that a direct relationship exists between bioactivity and enhanced bone formation. This bilayered bioactive-gradient coating promoted massive metaphyseal osseointegration, ensuring mechanical stability that should help prevent long-term complications such as ''stress-shielding'' or migration of wear debris.

Acknowledgments

The authors are grateful to Mireille Cottrel, Nadine Ferré, Isabelle Pavageau, Blandine Pilet, Jerome Constantin and Stephane Madec for technical assistance. This study was

supported by CPER Pays de Loire France and Zimmer France.

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Received 31 July
and accepted 31 October 2002