Clinical, radiological and histological evaluation of an osteoconductive interference screw containing 60 % β-TCP.

Results in 30 ACL reconstruction with the hamstring tendons at 1.5 year minimum follow-up.

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In my capacity of main author, I certify that all authors have seen and approved the manuscript being submitted and entitled "Clinical, radiological and histological evaluation of an osteoconductive interference screw containing 60 % β-TCP. Results in 30 ACL reconstruction with the hamstring tendons at 1.5 year minimum follow-up."
I warrant that the article is the authors' original work and that the article has not received prior publication and is not under consideration for publication elsewhere. On behalf of all co-authors, I recognize that shall bear full responsibility for the submission.

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Abstract

Purpose: The purpose of our study was to evaluate clinically, radiologically, and histologically the fate of resorption of an interference screw elaborated from an osteoconductive material (Ligafix 60®) containing 60% Tricalcium Phosphate and 40% poly-L-Lactic acid (PLLA) in anterior cruciate ligament (ACL) reconstruction with hamstring tendons.

Methods: We performed 30 ACL reconstructions with four-strand hamstring grafts (gracilis and semitendinosus) in 25 males and 5 females with an average age of 30 years (range, 15-54 years). A Rigidfix® system was used for femoral fixation, and a Ligafix 60® screw and a staple for tibial fixation. All patients were reviewed at 3, 6, 9, 12 and 18 months postoperatively. Laxity was assessed with a KT-1000 arthrometer and lateral radiographs were taken for comparison of the implanted screw to a control screw. X-rays were used to measure the density of both screws (density of screw core minus density of adjacent bone) using Adobe Photoshop 7.0. Then, we calculated the loss of radiological density at 3, 6, 9, 12 and 18 months postoperatively. Lastly, 7 biopsies of the screw-tendon and screw-bone interfaces were taken for studying screw resorption and graft anchorage.

Results: All the patients were followed for a minimum of one year. There was no aseptic fistula, but one screw fracture occurred at insertion. Mean laxity was 6.6 ± 1.4 mm preoperatively and 2 ± 2.2 mm postoperatively. Signs of degradation began to appear as soon as the first few months of implantation. After 6, 12 and 18 months, the composite screws had lost 63%, 78% and 83% of their initial density, respectively. Histological examination evidenced connective tissue at the screw-graft interface, followed by degradation of the implant and bone ingrowth. There was no persistent foreign body reaction.

Conclusion: The high ß-TCP content in the composite material seems to accelerate screw resorption and tendon anchorage without causing residual knee laxity or adverse reaction.

Level of evidence: Level IV

Keys words: interference screw; tricalcium phosphate; ACL; hamstring.

Introduction

In the nineties, metal screws were extensively used for anterior cruciate ligament reconstruction (ACL).[1] Such materials were then gradually replaced by absorbable poly-glycolic acid (PGA), and later by the poly-L-Lactic acid (PLLA) materials, which is now of common use. Absorbable screws provide fixation strength and clinical results similar to those of metal screws.[2] Metal screws have two mains disadvantages: they are difficult to remove in case of revision, and they produce artefacts on MRIs. The early degradation of PGA results in local synovitis [3,4] and absence of bone ingrowth [5]; interference screws of pure PGA are no longer used today. PLLA first undergoes slow fragmentation, and the degradation products are finally metabolized to carbon dioxide and water.[6] Release of polymers or monomers with free acid functions may induce more or less severe local osteolysis, particularly when the phagocytic capacities of macrophages are exceeded [33]. However, PLLA induces much less severe reactions with later onset than those induced by PGA. [5,7]

Many authors who used PLLA interference screws for ACL reconstruction found that PLLA was still present up to 4 years after implantation. [8,9,10,11] PLLA/ceramic (ß-TCP or hydroxyapatite) composite screws were first introduced in 2000; they were supposed to resorb more rapidly while retaining their initial mechanical properties until graft incorporation in the bone tunnels was observed. The potential influence of absorbable screws on tendon graft integration and their theoretical advantages in case of revision seem sufficient to justify their higher price.

We hypothesed that increased tricalcium phosphate content in the material can enhance screw resorption and favour bone ingrowth inside the tunnels.

Our purpose was to study the behaviour of a composite interference screw with high tricalcium phosphate content (60 % w/w) in ACL reconstruction using hamstring tendons. Our evaluation was based on the clinical assessment of knee stability, radiological density, and histological examination of biopsy specimens for evaluating foreign-body reaction, resorption of the screw and bone ingrowth.

Materials and Methods

1. Interference screw.

The screw Ligafix 60® (SBM, Lourdes, France) was manufactured by injection moulding. The material consisted of 60% ß-TCP (Tricalcium Phosphate) and 40% PLLA (poly-L-Lactic acid). TCP [$Ca_3(PO_4)_2$] was free of hydroxyapatite (HA) and calcium pyrophosphate as confirmed by x-ray diffraction analysis and infrared absorption spectrometry. The porous volume of the ceramic component was 36 ± 6%. At the time of implantation, cristallinity of the lactic acid polymer was over 80% as evidenced by chromatography, and molecular weight was over 70 kDa as defined by intrinsic viscosity[12]. The composite material was first evaluated in vitro and in vivo[13]. It demonstrated excellent biocompatibility, improved degradation kinetics, and gradual replacement by new bone tissue without any significant foreign body reaction when compared to pure lactic acid polymer[13] .

2. The series

This is a prospective single-center, single-surgeon study. Institutional review Board approval was obtained before initiating the study. All the patients, who gave their informed consent, with unilateral ACL injuries, between October 2003 and October 2004, were included in the study. Revisions of ACL reconstruction or patients who could not be followed for at least 18 months were excluded. Thirty consecutive ACL reconstructions were operated on in 25 males and 5 females with a mean age of 32 years (range, 15-54 years). All the patients were operated on several weeks after rupture of their ACL.

ACL reconstructions were performed arthroscopically using four-strand hamstring grafts. The "anatomical" cortico-cancellous Rigidfix® system (Mitek, Issy les Moulineaux, France) was used for femoral fixation. A Ligafix® 60 composite interference screw (SBM, Lourdes, France) and a staple were used for tibial fixation. Postoperatively, the patients wore a dynamic ROM knee orthosis allowing full weight bearing for one month. Rehabilitation consisted in closed chain kinetic exercises. Patients could resume running at 3 months and pivot sports after 9 months. All the patients were reviewed at 3 months, 6 months, 9 months, 12 and 18 months for clinical evaluation. Laxity was evaluated using the KT-1000 knee arthrometer (MEDmetric Corp, San Diego, Ca) at a maximum manual traction, and a lateral radiograph was taken.

***2.1** Radiological evaluation of resorption*

Radiological resorption was evaluated by comparing the radiological density of the implanted screw with a control screw (Ligafix 60®, diameter: 9 mm x length: 30 mm) that was taped to the skin of the leg, next to the tibial interference screw. Thus, both the implant and the control screw were radiographed using the same constants and the same x-ray equipment.

On each lateral digitized x-ray, image density was measured using Adobe Photoshop 7.0®. For each screw (implant and control), 6 measurements of grey level were taken in equal surface areas (Fig. 1) by two investigators :

- 2 in the screw core area (zones 1 and 2): the mean of these 2 values represented the radiological density within the implanted screw area : **D implant**
- 4 in the adjacent cancellous bone (zones 3, 4, 5, 6): the mean of these 4 values represented the radiological density of the adjacent bone: **D bone**

Actually, measurement of the **D implant** density also includes the density of the adjacent cancellous bone, so that density of the screw itself, **D screw,** was obtained by subtracting the density of adjacent bone from the density of the screw core: **D screw = D implant - D bone.** The same formula was used for the control screw, for which density is expressed as **D**

control. Finally, the loss of density **SR** was calculated as the relative difference between the radiological density of implanted and control screws using the formula:

SR = [1 - (D screw - D control) / D control] x 100 (%).

In order to check the correlation between screw resorption and loss of screw radiographic density, we measured the density of 5 screws with known resorption rates. The last step was the measurement of tibial tunnel width from the lateral x-ray at the intra-articular tibial tunnel aperture, using a protocol developed previously.[14] The change in shape of the tibial tunnel was classified according to one of the 3 descriptive categories: “core type, “line type” or “cavity type”. [15]

2.2 *Histology*

Biopsy specimens were taken inside the tibial tunnel at the screw-graft and screw-bone junctions during removal of the tibial staple. The specimens were immediately placed in undenatured alcohol. They were subsequently dehydrated in a graded series of ethanol solutions, transferred to acetone, and cleared in xylene. Some of the PLA group samples were left to dissolve in chloroform for a few hours and then transferred again to an absolute ethanol solution for 24 hours. They were placed in a methacrylate solution for 48 hours, and polymerized into polymethylmethacrylate (PMMA) in the presence of hydrogen peroxide. After polymerization was complete, 5 µm thick sections were taken and stained with Giemsa or Goldner solution. Evaluation of the tissue was performed under normal light.

3. Statistical methods

The values presented are the arithmetical mean of all the measurements (including extremes). For evaluation of screw density over time, we calculated the mean of R values for all the patients, for the considered period of time. The difference among the studied groups was evaluated using a Student's *t* test and then the Fisher's F-test, with less than 10% risk. Intra- and inter-operator repetitivity and reproducibility were evaluated using the analysis of variance (ANOVA).

Results

1. Clinical

The minimum duration of follow-up was 18 months (range, 18-30 months; average, 24 months). One screw fractured at the head-body junction during insertion at the beginning of our experience, without affecting initial stability of the graft. There were no aseptic fistulas or cysts at the entrance of the tibial tunnel. Mean laxity difference (side to side) as measured with a KT-1000 by the same investigator, decreased from 6.6 ± 1.4 mm preoperatively to 2 ± 2.2 mm at the last follow-up. In 93.3% of the patients, residual laxity was lower or equal to 5 mm (Fig. 2). Stability failed to be achieved (more than 5 mm laxity) in two patients (6.7% anatomic failure rate) who had to be revised with the Kenneth Jones technique at 1 year. Notchplasty was necessary for one patient to correct a 15° extension deficit.

2. Radiological

The first signs of degradation appeared within the first postoperative months. Density decreased, and the screw looked smaller, had blurred contours, and was sometimes curved. The residual screw image remains denser than that of the adjacent cancellous bone (Fig. 3).

The initially denser images of the tunnel walls at the screw-bone interface gradually became blurred, and were hardly visible after 6-12 months. At 6 months postoperatively, tunnel widening was not measurable in contact with the screw as tunnel walls were not distinctly visible. The free distal end of the tibial tunnel showed 31 ± 16% increase in diameter, with no further increase thereafter. All the tunnels had a “line type” contour when visible; we did not see any “core type” or “cavity type” that might indicate a severe inflammatory response at the periphery of the implant.

Results of the comparison between screws of known density and measurements of resorption showed a 98% (SD = 6.33) correlation, which validates that density as measured here is correlated to screw resorption (Fig. 4). Mean variation of the radiological resorption measured by the loss of density over time is presented on Fig. 5. It shows that the radiological resorption increases with time following a logarithmic trend. At 6, 12, and 18 months, the mean radiological resorption of the implant vs. control was 63 ± 21%, 78 ± 17%, and 83 ± 7% respectively. Mean standard deviation of repetitiveness was 5.37%, and mean standard deviation of reproducibility was 8.27%. There was no significant difference in the results of the two investigators, which confirms the effectiveness of this method in obtaining a reliable general trend.

2.3 Histological

Histological analyses were performed on 7 biopsy specimens obtained in 2 patients at 8-month follow-up, and in 5 patients at 11-month follow-up. Due to the small size of the samples, it was not possible to evaluate the histological degradation kinetics. These 7 screws could not be removed because they were macroscopically embedded in cancellous bone. Therefore, specimens could only be taken from the circumference of the extra articular part of the tibial tunnel. In one case, the head of a screw protruded out of the tibial tunnel, had degraded and became encysted: the intra tunnel portion of the screw had undergone bone remodeling. An additional screw was simply removed at 7 months postoperatively and seemed intact.

2.3.1. Bone-ligament interface and screw-ligament interface

At 8 months, in some areas, bone was thickened and eroded with surface proliferation of woven bone, and medullary spaces were filled with fibrous tissue, whereas in other areas, the very tight ligament-bone interface resembled Sharpey fibers (fig. 6). There was a tough connective tissue at the interface between the implant and the graft, bonding them with sufficient strength to resist tissue retraction that occurs during polymerization of the embedding polymer. In some places, fibers were oriented perpendicular to the surface of the material (fig. 6), also suggesting Sharpey fibers. Free ceramic particles were included in this fibrous tissue, which indicated an advanced state of degradation of the polymer matrix.

2.3.2. Screw-bone interface

At 8 months postoperatively, ingrowth of connective tissue containing a few or no cells was observed inside thin cracks of the implant, which began to resorb but maintained its initial shape. Connective tissue formation first occurs within these cracks, then predominantly around the different ceramic particles, building a network of thin canals filled by collagen and cells (fig. 7). The degradation of the screw takes predominantly place on the edge of the implant, as evidence by an irregular material surface, and around the inner TCP particles.

At 11 months postoperatively, screw fragmentation had occurred, evidencing higher resorption rate. The implant was penetrated by collagen bundles that reached the screw core (Fig. 8). Macrophage-like cells created an area of absorption of the polymer matrix around the ceramic particles. Direct ossification from this connective tissue can occur, leading to bone larger trabeculae invading the fragments of the implant, which had retained its overall shape. Such bone trabeculae have penetrated inside the screw and can be observed lining the central lumen of the implant. There was cancellous bone in direct and intimate contact with the implant over most of its perimeter, with no entrapped macrophages.

Discussion

Direct interference screw fixation of hamstring tendons does not have the same static and dynamic strength as tendon fixation with attached bone plugs. And yet, initial mechanical strength is critical pending biological fixation within bone tunnels[16].

The graft is fixed to the tunnel walls by Sharpey fibers (indirect fixation), and to the tunnel aperture by a chondral-apophyseal ligament insertion (direct fixation)[17,18]. Initially, a fibro vascular interfacial tissue is formed between the graft and bone. This stage is followed by gradual re-establishment of collagen fiber continuity, and newly formed bone is visible after a few weeks. Sometimes, a fibrochondral tissue area is observed, as direct fixation occurs. Tendon graft integration depends on environmental factors (type of fixation, tension on the graft, filling of the tunnel), anatomic regions, and also, most probably, on individuals. The absence of tendon graft integration due to faulty fixation may cause failure of the reconstruction[19,20]. Tendon graft fixation within the bone tunnel takes at least 12 weeks [7,21] and probably much longer.[19,22] However, this process can be accelerated by graft compression[18].

Slow degrading screws are unable to contribute to anchorage, and can delay tissue healing. Therefore, there is a theoretical advantage to using fast degrading screws and their osseous replacement which may indirectly provide tendon graft fixation. We have observed direct and resistant connective tissue attachment on the surface of the screw (fig. 6). It is generally believed that reduction of graft micro motions in the tunnel due to early anchorage is likely to promote graft aperture fixation and reduce tunnel enlargement[18,23].

We chose to use a composite material containing tricalcium phosphate rather than hydroxyapatite (which resorbs very slowly), with a high TCP content of 60% versus 10-30% in the other currently available screws. Prior study results do not show a higher fracture risk with this type of screw than with screws having a ceramic content of 20-30%[13]. In our series, we only had one screw head fracture during screw insertion, without incidence on the stability of the graft. Barber et al. reported 7% screw fracture during insertion of 7 mm diameter screws[24]. The improved design of the screwdriver tip and the deeper screw head drive have resulted in a lower fracture rate[20]. The rapid degradation kinetics of this composite material had made us fear tendon graft slackening due to micro motions within the bone tunnels. In fact, we have had 6.7% of side to side laxity greater than 5 mm in our series, which is very close to the rate reported in other publications[25]. The faster resorption of the evaluated screws has not resulted in increased laxity, which could have logically been feared. Osteolysis at the tunnel aperture with resulting enlargement of the tunnel is a common complication associated with any type of screw. The mean percentage of enlargement at the tibial tunnel aperture was 31 ± 16%, which is consistent with the results in other series, in the same measurement conditions (26 ± 17% for Insalata, 22 ± 20% for Webster). Increased density at the margin of the tunnels, although not calculated here, is much lower than that reported in a previous study with a PLLA screw[14]. This is consistent with Robinson's findings in a study on a PLLA-HA screw, in which the tunnel walls rapidly became very thin and then invisible[28]. In this study, tunnel walls gradually became blurred and hardly visible after 10-12 months, suggesting advanced bone healing at the bone/screw interface.

The mean resorption of the screws were 78% at 1 year, and 83% at 18 months. Drogset et al. measured the resorption of PLLA screws by calculating the residual volume of screws from MRI images[8]. At 2 years, there was a mean loss of volume of 64%. Morgan et al. reported a loss of molecular mass of 75% at 2.5 years.[10] However, these two series concerned bone plug fixation, contrastingly, Radford et al., who studied direct screw fixation of hamstring tendons, did not report any loss of volume at 4-year follow-up[11]. Therefore, it appears that environment is critical to the resorption process. As a matter of fact, if the screw is not fully included in the bone tunnel, it becomes encysted but it is not absorbed (one case in the series); this also applies to unstable or mobile screws, which probably explains the necessity of removing a non-ingrown screw at 7 months. These facts support the hypothesis that early bone ingrowth can occur, without encapsulation, when there is direct contact and stability of the screw.

The 7 biopsies performed in this work provide valuable information on behaviour of the evaluated composite screw versus screws made of pure PLLA. In our study, the composite screw-tendon graft interface is free of encapsulation membrane (which includes many macrophages) contrary to the interface with pure PLLA screws[19,20], which confirms the safety of this composite material[9,10]. The graft tissue is firmly bonded to the surface of the material, thus probably ensuring stable and durable secondary fixation. At the same time, the composite material is severely eroded (several hundreds of microns), penetrated by collagen bundles and then fragmented; new bone trabeculae have been found within the implant. In the preliminary experimental study, we had demonstrated the direct correlation between osteoblastic activity and dissolved calcium and phosphate ion content[13]. The released Ca^{++} ions activate specific receptors in osteoblasts, which promote their migration and proliferation[20]. Initially, degradation seems to occur next to ceramic particles, as seen in the cavities (which contain macrophages) surrounding the β-TCP granules and are interconnected by thin tunnels. Ingrowth of connective tissue into these areas seems to provide stable mechanical fixation and surely indicates beginning of resorption.

This resorption/bone formation process may explain why a bone density image persists on x-rays and why resorption reaches a maximum level of approximately 90% after 1.5 year of implantation. This corresponds to Grade 4 resorption according to Pistner's classification.[30] When Grade 5 resorption is reached, the polymer is no longer detectable and has been replaced by fibrous tissue or bone. The amount of newly formed bone observed at 1 year is close to that reported with polyglycolic acid (PGA) pins of a much smaller size, after 6 months of implantation but there is no osteolytic response[31]. This is a fundamental difference that is probably due to two factors: the absence of acidification of the medium owing to the lesser amount of PLLA being hydrolyzed (the material contains only 40% PLLA), and the basic behaviour of tricalcium phosphate which might act as a buffer, permitting healing by osteoconduction. Degradation of the composite equally involves PLLA and TCP, thus allowing maintenance of a neutral pH, which is known to enhance bone formation, since degradation of pure PLA materials into lactic acid results in acidification of the medium and promotes encapsulation of the material.

To our knowledge, only one clinical study has described the outcome of a PLLA-HA composite screw[32]. At 2 years, fragmentation occurs, and the screw is surrounded by lymphocytes, giant cells and fibrocytes. There is no fixation of the tendon graft to the screw. As far as we know, other currently available composite screws (*i.e.* PLLA + TCP or HA or calcium carbonate) have not been histologically studied in humans.

The histological study has its limits: the biopsies taken from the extra articular part of the tunnel does not reflect the behaviour of the entire screw at the aperture.

Conclusions

The PLLA-TCP composite interference screw containing 60 % β-TCP evaluated in this study is, to the best of our knowledge, the first screw to be gradually resorbed and partly replaced by bone while developing tight attachment to the graft without adverse tissue reaction at 1.5 year follow-up. Such events might be of significance for reducing short term laxity of the plasty and delayed inflammatory reaction.

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Legends

Figure 1. Technique for measuring the radiographic density of 6 different areas in each screw: roughly circular areas are selected in 6 different places (zones 1 and 2 in the screw core, zones 3 to 6 in the adjacent cancellous bone) on lateral view, and the grey level density of each area is measured inside each area. The mean of the values obtained in the adjacent bone is defined by the formula D bone = (zones 3+4+5+6) / 4, the mean of the values obtained in the screw core is defined by the formula D implant = (zones 1+2) /2, and the density within the screw is D screw = D implant - D bone. The same formula was used for the control screw

Figure 2. Preoperative (black) and postoperative (white) side to side laxity (in millimeters) obtained with KT-1000 at a maximal manual traction.

Figures 3. Lateral views of the tibia taken at 2, 4 and 12 months postoperatively. 3a : the screw is clearly visible and no change is noted. 3b: the screw has blurred contours, decreased density. 3c: the screw is hardly visible, but the image of the residual screw persists as a slightly dense area.

Figure 4. Correlation between theoretical resorption and radiological measured density; error bar is the standard deviation (correlation coefficient = 0.98).

Figure 5. Variation of radiological density relative to period of implantation. Error bar is the standard deviation.

Figure 6. Biopsy of the graft. The collagen tissue (CT) of the graft is fixed to the bone (B) and the implant (I) by fibers suggesting Sharpey's fibers. Giemsa staining

Figure 7: Biopsy of the screw taken at 8 months, showing penetration of the implant by collagen fibers which bridge the TCP particles. Giemsa staining

Figure 8. Photocomposition of a cross-section of a screw at 11 months. The implant (PLA/TCP) is fragmented and penetrated by cancellous bone. In the windows, higher magnification of the canal network filled by connective tissue in the implant matrix. It can occur a direct ossification (B) from this connective tissue (CT). Bone trabeculae have penetrated inside the screw and can be observed lining the central lumen of the implant Giemsa staining

Figure 1. Technique for measuring the radiographic density of 6 different areas in each screw: roughly circular areas are selected in 6 different places (zones 1 and 2 in the screw core, zones 3 to 6 in the adjacent cancellous bone) on lateral view, and the grey level density of each area is measured inside each area. The mean of the values obtained in the adjacent bone is defined by the formula D bone = (zones 3+4+5+6) / 4, the mean of the values obtained in the screw core is defined by the formula D implant = (zones 1+2) /2, and the density within the screw is D screw = D implant - D bone. The same formula was used for the control screw.

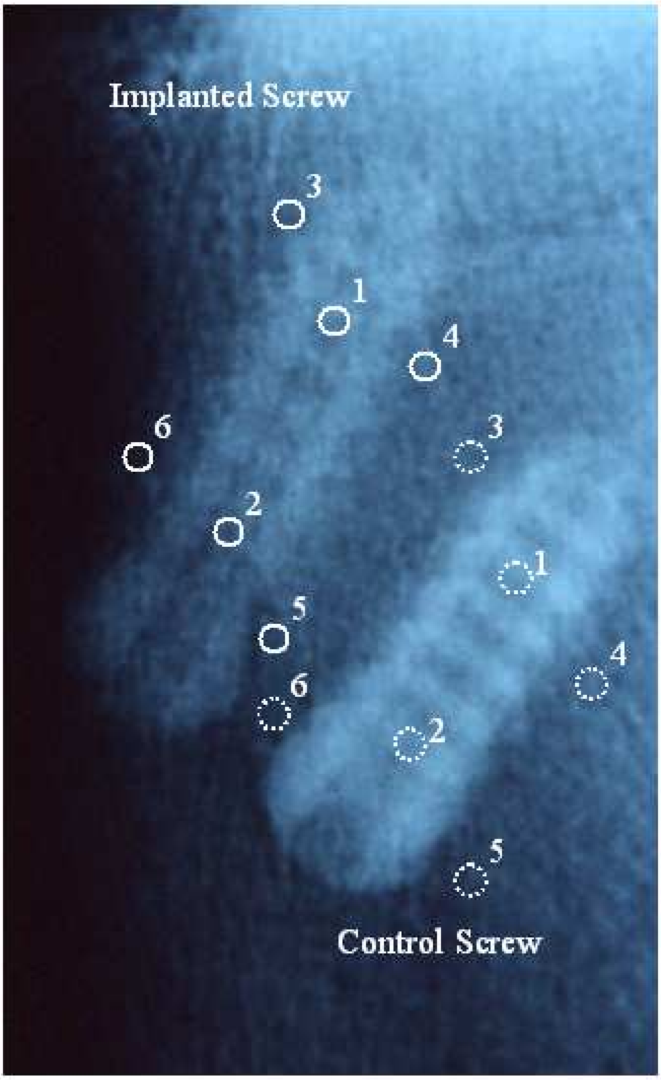


Figure 2. Preoperative (black) and postoperative (white) side to side laxity (in millimeters) obtained with KT-1000 at a maximal manual traction.

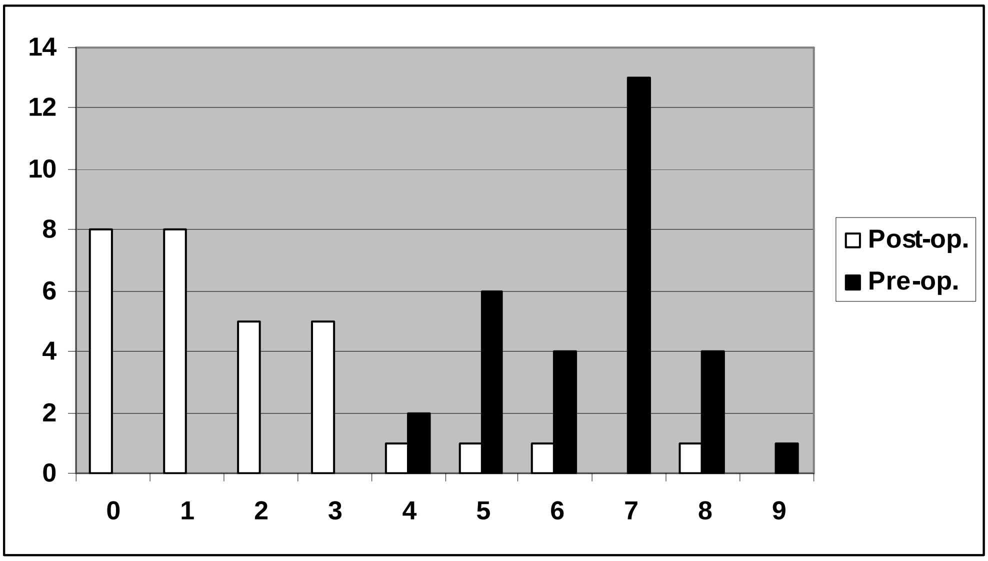
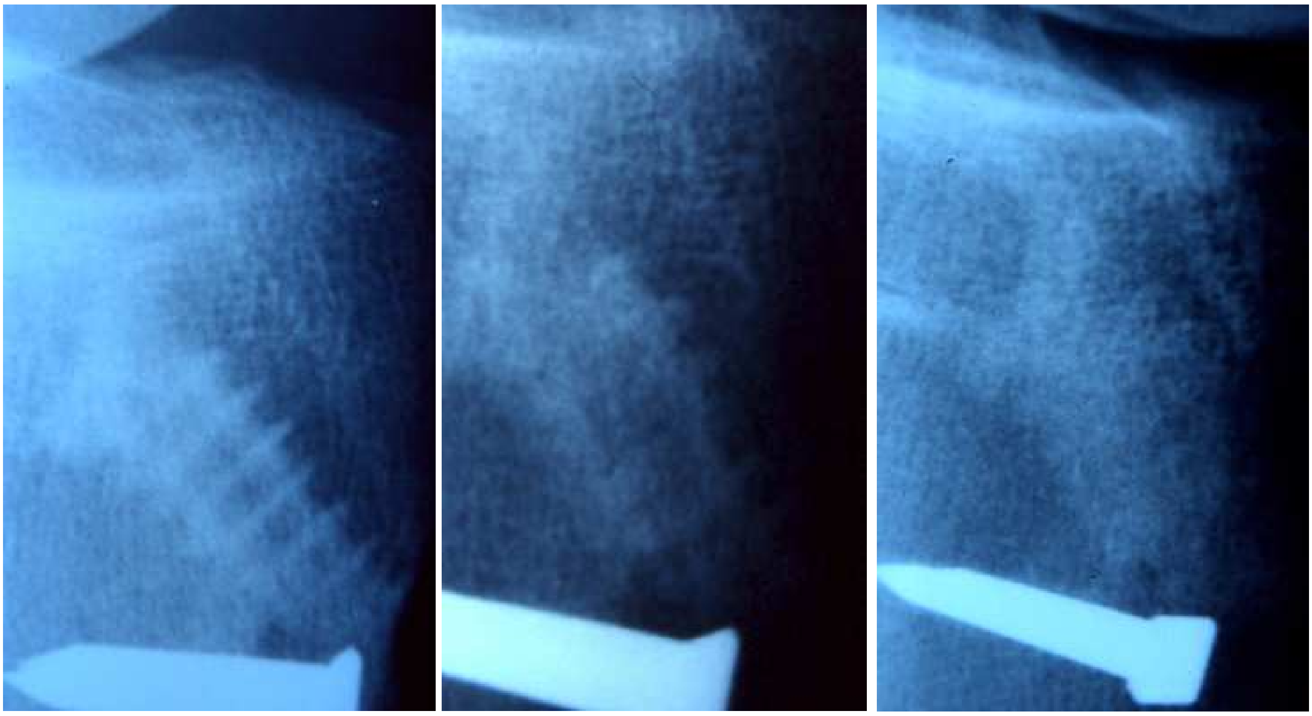


Figure 3. Lateral views of the tibia taken at 2, 4 and 12 months postoperatively. 3a : the screw is clearly visible and no change is noted. 3b: the screw has blurred contours, decreased density. 3c: the screw is hardly visible, but the image of the residual screw persists as a slightly dense area.



3a 3b 3c

Figure 4: Correlation between theoretical resorption and measured radiological resorption ; error bar is the standard deviation (correlation coefficient = 0.98).

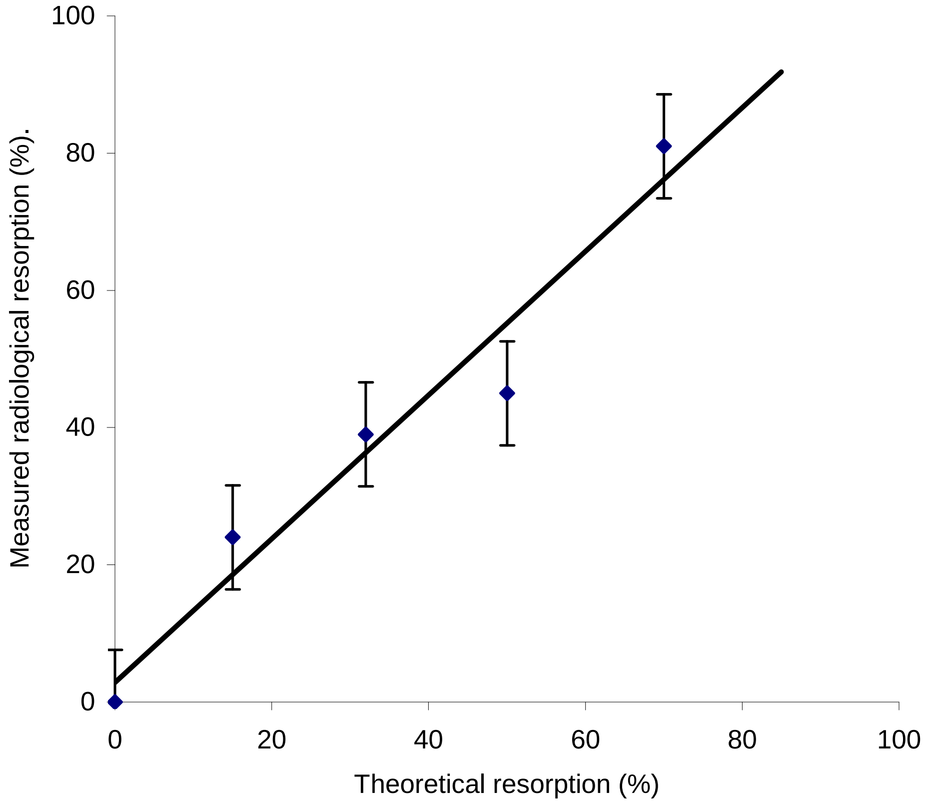


Figure 5. Variation of radiological resorption relative to period of implantation. Error bar is the standard deviation.

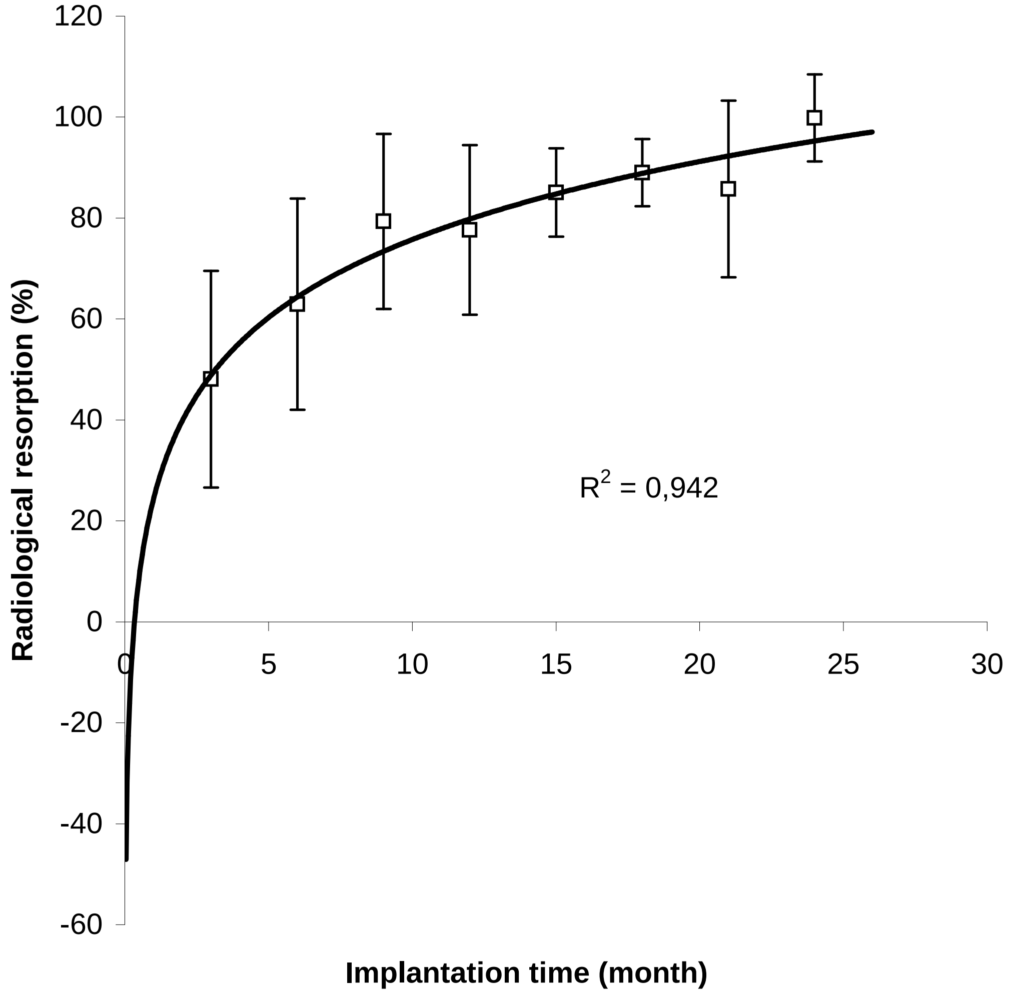


Figure 6. Biopsy of the graft. The collagen tissue (CT) of the graft is fixed to the bone (B) and the implant (I) by fibers suggesting Sharpey's fibers. Giemsa staining

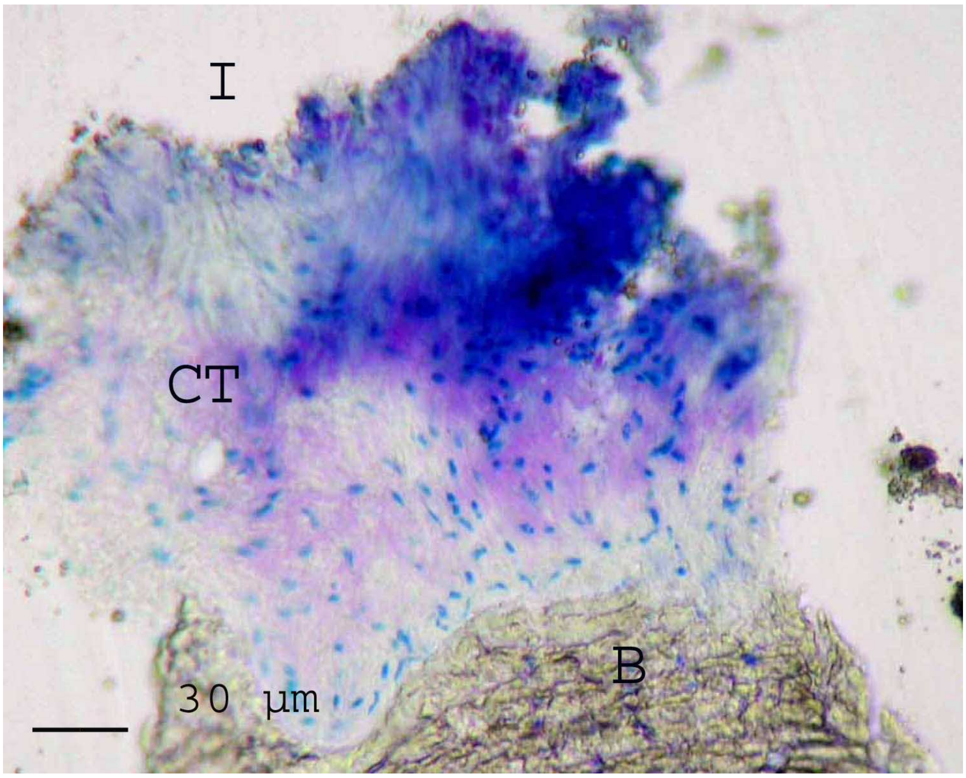


Figure 7. Biopsy of the screw taken at 8 months, showing penetration of the implant by collagen fibers which bridge the TCP particles. Giemsa staining

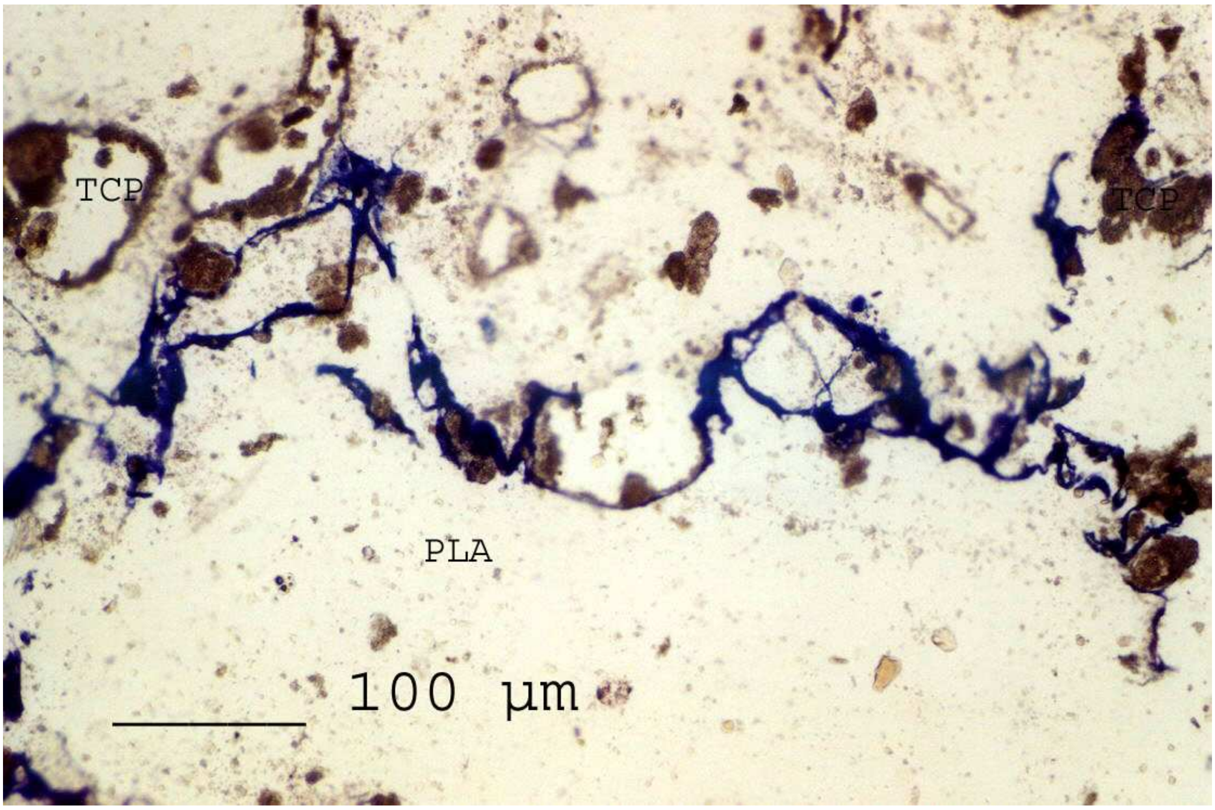


Figure 8. Photocomposition of a cross-section of a screw at 11 months. The implant (PLA/TCP) is fragmented and penetrated by cancellous bone. In the windows, higher magnification of the canal network filled by connective tissue in the implant matrix. It can occur a direct ossification (B) from this connective tissue (CT). Bone trabeculae have penetrated inside the screw and can be observed lining the central lumen of the implant Giemsa staining