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Prediction of bone density around orthopedic implants delivering bisphosphonate

Vincent A. Stadelmann [a], Alexandre Terrier [a], O. Gauthier [b], J.-M. Bouler [b], Dominique P. Pioletti [a,*]

[a] Laboratory of Biomechanical Orthopedics, Institute of Bioengineering, Ecole Polytechnique Fédérale de Lausanne, 1015 Lausanne, Switzerland
[b] Nantes Atlantique Universités, INSERM UMR 791, LIOAD, BP 84215, 44042 Nantes, France

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ABSTRACT

The fixation of an orthopedic implant depends strongly upon its initial stability. Peri-implant bone may resorb shortly after the surgery. This resorption is directly followed by new bone formation and implants fixation strengthening, the so-called secondary fixation. If the initial stability is not reached, the resorption continues and the implant fixation weakens, which leads to implant loosening. Studies with rats and dogs have shown that a solution to prevent peri-implant resorption is to deliver bisphosphonate from the implant surface.

The aims of the study were, first, to develop a model of bone remodeling around an implant delivering bisphosphonate, second, to predict the bisphosphonate dose that would induce the maximal peri-implant bone density, and third to verify *in vivo* that peri-implant bone density is maximal with the calculated dose.

The model consists of a bone remodeling equation and a drug diffusion equation. The change in bone density is driven by a mechanical stimulus and a drug stimulus. The drug stimulus function and the other numerical parameters were identified from experimental data. The model predicted that a dose of 0.3 μg of zoledronate on the implant would induce a maximal bone density. Implants with 0.3 μg of zoledronate were then implanted in rat femurs for 3, 6 and 9 weeks. We measured that peri-implant bone density was 4% greater with the calculated dose compared to the dose empirically described as best.

The approach presented in this paper could be used in the design and analysis processes of experiments in local delivery of drug such as bisphosphonate.

1. Introduction

The fate of orthopedic implants seems to be principally determined at an early stage. Rapid early migrations of stems have been detected in many asymptomatic hips, often as early as 4 months postoperatively (Karrholm et al., 1994). These early migrations have been related to an increased risk of clinical loosening. It has been reported that peri-implant bone resorbs during a short period after the surgery, probably in response to the surgically induced trauma, inducing a weakening of the fixation (Venesmaa et al., 2001). In normal healing conditions, the fixation strength increases after this initial weakening (Dhert et al., 1998), but in pathologic conditions, the lack of initial fixation promotes osteolysis via bone-implant micromotions production, debris particulate formation and osteoclastic resorption e.g. Stadelmann et al. (2008).

Based on current knowledge regarding early biological events at the implant interface, it has been proposed to use bisphosphonate to improve the early implant fixation by preventing the post-surgery osteoclastic resorption (Horowitz and Gonzales, 1996). A recent clinical study showed that post-surgical systemic administration of clodronate prevents knee prosthesis migration (Hilding and Aspenberg, 2006). Systemic administration of bisphosphonate presents several adverse effects, like fever, ulcers and osteonecrosis of the jaw (Dannemann et al., 2007). Since bones are low-perfused organs, drugs diluted in blood stream have low probabilities to reach the required locations with sufficient time or concentration to be effective. To ensure the availability of bisphosphonate at the peri-implant area, where it is most needed, methods for local delivery have recently been addressed (Wermelin et al., 2007; Peter et al., 2006, 2005). According to these studies, the effect of bisphosphonate released from implants is non-linearly dose dependent.

In order to calculate the optimal bisphosphonate dosage to obtain the best implant fixation, a biophysical theory of the events arising around an implant used for a local delivery of

* Corresponding author. Tel.: +41 21 693 83 41; fax: +41 21 693 86 60.
E-mail address: dominique.pioletti@epfl.ch (D.P. Pioletti).

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bisphosphonate is needed. Such a theory must relate bone remodeling to both the mechanical aspects of peri-implant situation and the effect of the bisphosphonate. Most of the existing models of bone remodeling are mechanically driven e.g. Huiskes et al. (2000). Few attempts exist to address the effect of systemic bisphosphonate using a model of remodeling (Hernandez et al., 2001; Pioletti and Rakotomanana, 2004). However these attempts did not take into account the spatial diffusion of bisphosphonate when released from a local source. Therefore, the goals of the present study were triple: first, to develop a model of bone remodeling including mechanical stimulus as well as the stimulus of bisphosphonate diffusing from an implant; second, to identify the parameters of the model from published data; and third to validate the model by verifying its prediction *in vivo*.

2. Materials and methods

2.1. Theoretical developments

The following developments were based on an existing bone model of remodeling previously developed in our group (Terrier et al., 2005). We extended the initial model by adding a new internal variable for the drug concentration. The bone density evolution law was adapted to include this new variable and finally we introduced a diffusion law for the drug. In the initial model of remodeling, the local bone density ϕ varies under the influence of a mechanical stimulus ψ. The choice for this stimulus was the plastic yield stress of Hill (Rakotomanana et al., 1992). According to this choice, it has been shown that the dependence of the stimulus in the density ϕ could be written in the following form $\psi = Y/\phi^4$ (Terrier et al., 2005), where Y is a mechanical function that only depends on the stress, but may, however, depend on space and time through the stress. The bone density evolution law was characterized by three different regimes: resorption, equilibrium and densification, according to the stimulus level. In the present study, the extension of the initial model was limited to the densification regime. According to the evolution law (Eq. (1)), bone cells produce extracellular matrix when the stimulus exceeds a densification stimulus threshold ψ_d.

$$\partial_t \phi = \upsilon_d(\psi - \psi_d) \tag{1}$$

The rate of densification is given by the constant υ_d, which was determined from experiment in rats (Terrier et al., 2005).

The extension of the initial model consists in adding the net effect of the drug as an imbalance of the remodeling process, resulting in a net gain in bone mass. This effect was introduced through a second stimulus Φ_{drug}, called drug stimulus, which was defined as a function of a new internal variable, the local drug concentration κ. The model was limited by the following hypothesis: (i) the drug stimulus depends only on the drug concentration (ii) the mechanical stimulus does not depend on the drug concentration, and (iii) the bisphosphonate diffuses following the Fick's law of diffusion.

The drug stimulus $\Phi_{drug}(\kappa)$ is expressed in (% change day^{-1}), and the drug concentration κ in (μg/mm^3). The rate of densification (Eq. (1)) becomes

$$\partial_t \phi = \upsilon_d(Y/\phi^4 - \psi_d) + \Phi_{drug}(\kappa) \tag{2}$$

completed by drug diffusion

$$\partial_t \kappa = \nabla(D\nabla\kappa) \tag{3}$$

where D is the effective coefficient of diffusion, which takes into account the diffusion of the drug into bone marrow, and the tortuosity of cancellous bone.

2.2. Identification of the model's parameters

The unknown parameters of the model are the diffusion coefficient D, the mechanical function $Y(x)$ and the drug stimulus function $\Phi_{drug}(\kappa)$.

First, we experimentally estimated that $D \cong 800$ (μm^2/day) with an experimental setup using C14-zoledronate diffusing through trabecular bone (Tb) sections (Peter, 2004).

To identify the other parameters, we used previously published bone density profiles measured around drug-releasing implants (Peter et al., 2005). These profiles were obtained with five different doses of bisphosphonate, zoledronate in this case (0, 0.2, 2.1, 8, 16 μg/implant) corresponding to (0, 0.034, 0.35, 1.43, 2.7 μg/mm^3) grafted onto the hydroxyapatite (HA) coating of cylindrical titanium implants in rat condyles at 3 weeks post-op. We simplified the system of equations (Eqs. (2) and (3)) with regards to this particular experimental setup, with the following assumptions: first, we reduced the system to a one-dimensional axisymmetric geometry, where x is the distance from the coating. Second we idealized the boundary conditions by assuming that (i) the hydroxyapatite coating is an infinite source of bisphosphonate, i.e., $\kappa(x = 0,\ t) \equiv \kappa_0$, and (ii) at 2 mm from coating the drug concentration is null i.e., $\kappa(x = 2000, t) \equiv 0$ (Fig. 1).

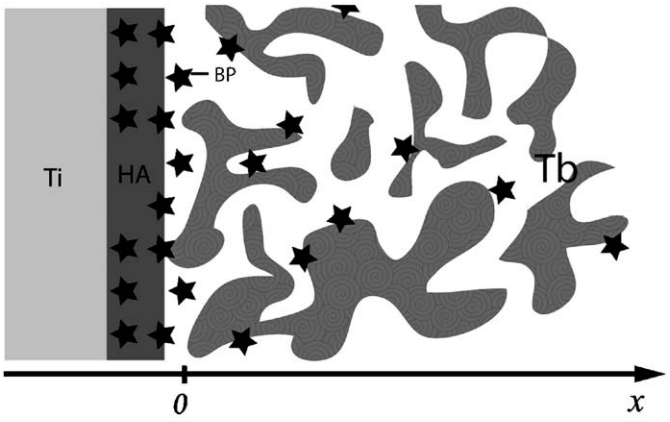

Fig. 1. Simplified scheme of the experimental system: the titanium implant (Ti) is coated with a thin layer of hydroxyapatite (HA). Bisphosphonate molecules (stars) initially loaded in the hydroxyapatite coating are slowly released, diffuse in the peri-implant trabecular bone (Tb) and influence the remodeling locally. The bisphosphonate concentration and the bone density are functions of the distance x from the coating.

According to these assumptions we estimated the mechanical parameter $Y(x)$, by solving the evolution equation (Eq. (2)) for the control group without drug stimulus. In the following calculations, we further assumed that $Y(x)$ is the same for all groups, which is reasonable since it only represents the stress state. Finally, we calculated the drug stimulus $\Phi_{drug}(\kappa)$ from the bone density at the coating surface, where drug concentrations can be assumed to be constant and equal to that of the coating, for the five different drug concentrations used in the *in vivo* data (Peter et al., 2005). The validity of these assumptions is discussed below.

The bone density was then calculated from the model as a function of the distance from the coating and is represented in Fig. 2. The calculated density profiles are very similar to the experimental data. The error between experimental data and calculated data was estimated as the mean relative difference in bone density for $0 < x < 150$ μm and was smaller than 5% for each bisphosphonate concentration. Computations were processed with custom-made routines of *Mathematica* (Wolfram Research, USA).

2.3. Validation of the model

The verification of the model was done in two steps. First, we evaluated the bisphosphonate dose which theoretically induces the maximal peri-implant bone density. We refer to this dose as the "optimal dose" in the following. In the second step, we verified that this optimal dose induced *in vivo* the maximal peri-implant bone density in a rat model. The *in vivo* methods used in this part were adapted from (Peter et al., 2005).

2.3.1. Estimation of the optimal concentration

To calculate the optimal drug dose, we solved the theoretical model, with zoledronate concentration as the variable, to maximize the bone density over a thickness of 100 μm from the coating: $Max_\kappa \int_0^{100\,\mu m} \phi(x,\kappa)\,dx$, and we found that $\kappa_{opt} = 0.044$ μg/mm^3 corresponding to 0.3 μg/implant. With this drug dose we calculated that the average bone surface/total surface (BS/TS) in the 100 μm proximity of the implant would be BS/TS = 61.6, i.e., 2% greater than the highest density measured so far with 2.1 μg/implant.

2.3.2. Implants

Twelve titanium alloy cylinders (diameter 3 mm; length 5 mm) were plasma-coated with hydroxyapatite and then six implants were soaked in aqueous solutions of 3×10^{-6} and six implants in 2.25×10^{-5} mol L^{-1} of zoledronate (Novartis Pharmaceuticals AG, Switzerland) for 48 h. The amount of zoledronate loaded onto the implants was measured to be, respectively, 0.3 and 2.1 μg.

2.3.3. Rats

Twelve female 6-month-old Wistar rats were used in this experiment. The animals had free access to normal diet. The animals were randomly separated into six different groups representing the two zoledronate doses: 0.3 and 2.1 μg/implant and three time points: 3, 6 and 9 weeks (Table 1). Each rat received one implant in a femoral condyle.

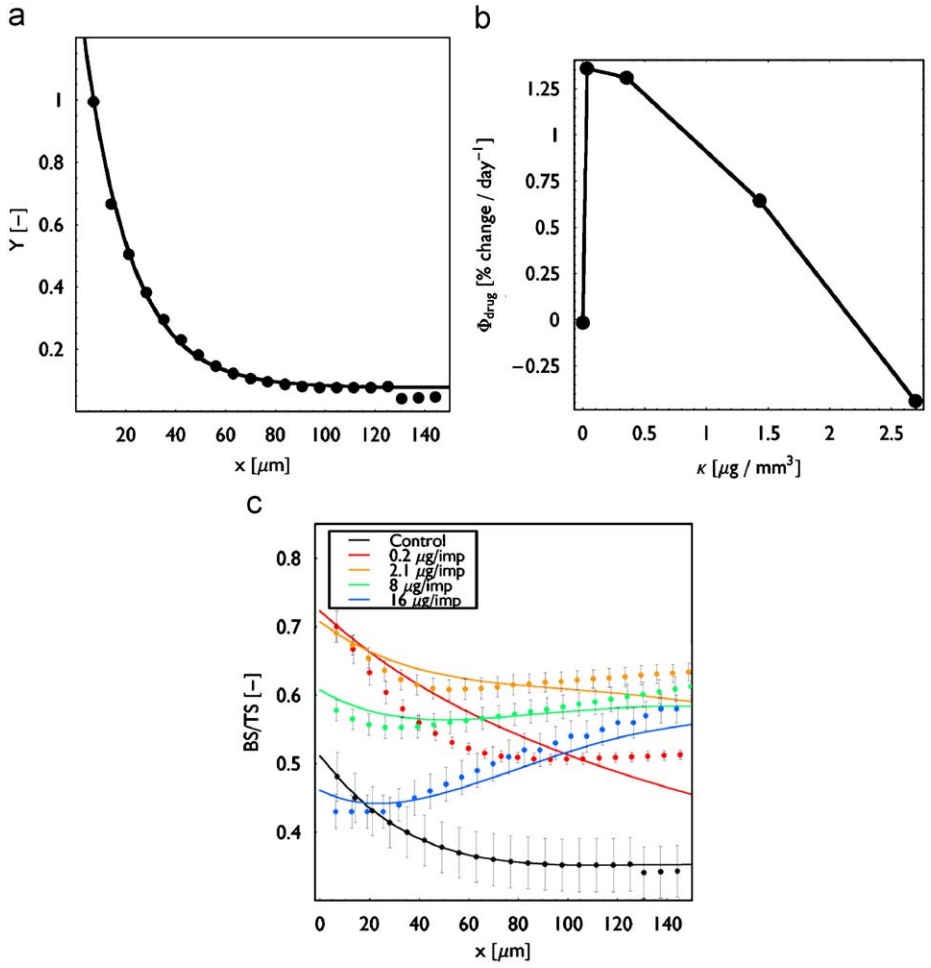

Fig. 2. (a) $Y(x)$ as a function of x as calculated from the data (points) and the continuous interpolation used for numerical computations (line). (b) The drug stimulus as a function of drug concentration (points), and the continuous interpolation used for numerical computations (line). (c) Bone density (BS/TS) as a function of the distance from coating: experimental (points) and model (lines) for the different drug concentrations.

Table 1
Number of animals per group.

Dose (μg/implant)	3 w	6 w	9 w
0.3	2	2	2
2.1	2	2	2

2.3.4. Surgery

The local Ethical Committee for Animal studies of the National Veterinary School of Nantes approved the protocol for the animal experiment. Animals were kept at the Experimental Surgery Laboratory of the Nantes University according to the European Community guidelines for the care and use of laboratory animals (DE86/609/CEE).

Surgical procedures were conducted under general anaesthesia. The implantations were performed at the distal end of the femurs, at the epiphysometaphyseal junction. The lateral condyle was exposed and drilled perpendicularly to the long axis of the femur with two successive bits (2.2 and 2.8 mm in diameter) on a low-speed rotative dental handpiece and under sterile saline irrigation. The implant was then gently inserted into the cavity under digital pressure. Articular and cutaneous tissues were closed in two separate layers. After surgery, all the animals were allowed to move freely in their cages. Animals were killed 3, 6 or 9 weeks after implantation by intracardiac injection of overdosed sodium pentobarbital under general anaesthesia.

2.3.5. Preparation for imaging

The femoral ends were then immediately dissected, fixed in glutaraldehyde solution, and stored in a 4% paraformaldehyde, 0.1% glutaraldehyde in 0.08 M cacodylate buffer. The sample was dehydrated in a series of alcohol solutions. For the impregnation, the sample was soaked in a mixture of 50% alcohol 1008 and 50% methyl methacrylate (MMA) (Fluka Chemika, Sigma Aldrich Chemie Gmbh, Steinheim, Germany) during 24 h then in pure MMA during 24 h. For the inclusion, the sample was soaked during 2 h under vacuum in a solution containing 90% MMA, 10% dibutylphtalate and 1% benzoyl peroxide (Fluka Chemika), then soaked in the same solution but enhanced by a polymerization activator (*N*,*N*-dimethyl-*p*-toluidine) (Fluka Chemika). The polymerization took place at −20 °C during 48 h. Three to four slices of 300-μm-thick perpendicular to the implant were cut from each sample, using a Microtome saw 1600 (Leica, Nussloch, Germany) diamond saw.

2.3.6. Scanning electron microscopy (SEM)

The slices were carbon-coated. The samples were then observed in a JEOL JSM 6300 scanning electron microscope (JEOL, Tokyo, Japan) using the backscattered electron detector allowing distinguishing mineralized bone from soft tissue. Then, these images were used to measure the bone density as a function of the distance from the coating. The implant surface and trabecular bone regions were defined manually on each image. To distinguish bone from other tissues: pixels with gray level between 0 and 62 were considered as calcified bone, while those with gray level from 63 to 255 were considered as other tissues. We defined successive regions of interests inside the trabecular bone in the form of series of ten 20-μm-thick arcs co-centered with the implant. In each arc, the number of bone pixels was counted and the bone density was defined as bone pixels divided by total pixels in the arc (BS/TS), using custom algorithms developed with *ImageProcessing* for *Mathematica.*

2.3.7. Statistics

The number of slices per animal was accounted for as repetition of density measurement of the same animal. The mean and the standard error of the mean for the two animals used in each group are presented.

3. Results

3.1. In vivo verification of model's predictions

The model predicted that a drug dose of 0.3 μg/implant maximizes bone density within 100 μm layer around the implant. To verify this prediction, bone density was measured *in vivo* with 0.3 μg/implant and 2.1 μg/implant zoledronate at 3, 6 and 9 weeks in rat condyles. These measures were compared to previous measures with 0, 0.2 2.1, 8 and 16 μg/Zoledronate/implant from (Peter et al., 2005).

One rat in the 3 weeks—2.1 μg zoledronate group and one rat in the 9 weeks—0.3 μg-zoledronate group were excluded from further analysis, as, for unknown reasons, the implant was not integrated into bone. A total of thirty-three slices were analyzed (Table 2).

At three weeks, the model's predictions were verified. The mean bone density of the group with optimal zoledronate dose was 4% greater than the highest bone density obtained so far in our previously published results (Fig. 3a). The mean bone density with 2.1 μg zoledronate/implant was in the range of our previous data. The difference in bone density between the 0.3 μg/implant group and the 2.1 μg/implant group observed at 3 weeks, was no longer observed at 6 and 9 weeks (Fig. 3b).

3.2. Evolution of the integration of the implant

The SEM observations confirmed implant integration comparable to that previously described (Fig. 4a). The hydroxyapatite coating evolved at the different time points after implantation. At 3 weeks, the bone was in contact with the coating surface, but there was no sign of resorption in the coating and almost no bone entering the coating (Fig. 4b). At 6 weeks, the first signs of resorption appeared in the coating. Approximately half of the thickness of the coating had been resorbed and lacunae could be observed *in* the coating (Fig. 4c). At 9 weeks, most of the coating had been resorbed and newly formed bone was in contact with the titanium surface. Lacunae were still present inside the coating and some speckles of bone grew directly from the implant surface (Fig. 4d).

Table 2
Number of slices for imaging per group.

Dose (μg/implant)	3 w	6 w	9 w
0.3	6	8	3
2.1	3	6	6

4. Discussion

The principal aims of this projects were first, to develop a theoretical framework of bone remodeling influenced by local release of bisphosphonate; second, to identify the parameters of the model and third, to verify the model's predictions *in vivo*.

The development of the model consisted of adding the drug concentration as a new internal variable to an existing model of remodeling, completed by a function relating the drug concentration to the remodeling stimulus. The parameters appearing in this new model were identified from our previously published experimental data (Peter et al., 2005). Next we solved this model to predict that a dose of 0.3 μg of zoledronate grafted on the implant coating would maximize the peri-implant bone density. This prediction was finally confirmed experimentally: with this calculated dose, the bone density was maximal, compared to other doses, at 3, 6 and 9 weeks post-op.

The intensity of the effect of bisphosphonate is dose dependent. The theoretical framework developed here shows that the interpretation of bone density profiles has to take into account the mechanical situation, the drug diffusion and the effect of drug on the remodeling balance, modeled here by the drug stimulus Φ_{drug}.

The drug stimulus function is the key point of the model. It can be interpreted as the signature of the drug in a particular animal model. The shape of this function reflects that the drug induces the imbalance of the remodeling process after the decrease of osteoclast activity. The shape of the function is concordant with what is observed *in vitro*: bisphosphonates, like most drugs, have a range of concentration with beneficial effects but can produce adverse effects at higher doses (Fleisch, 2002).

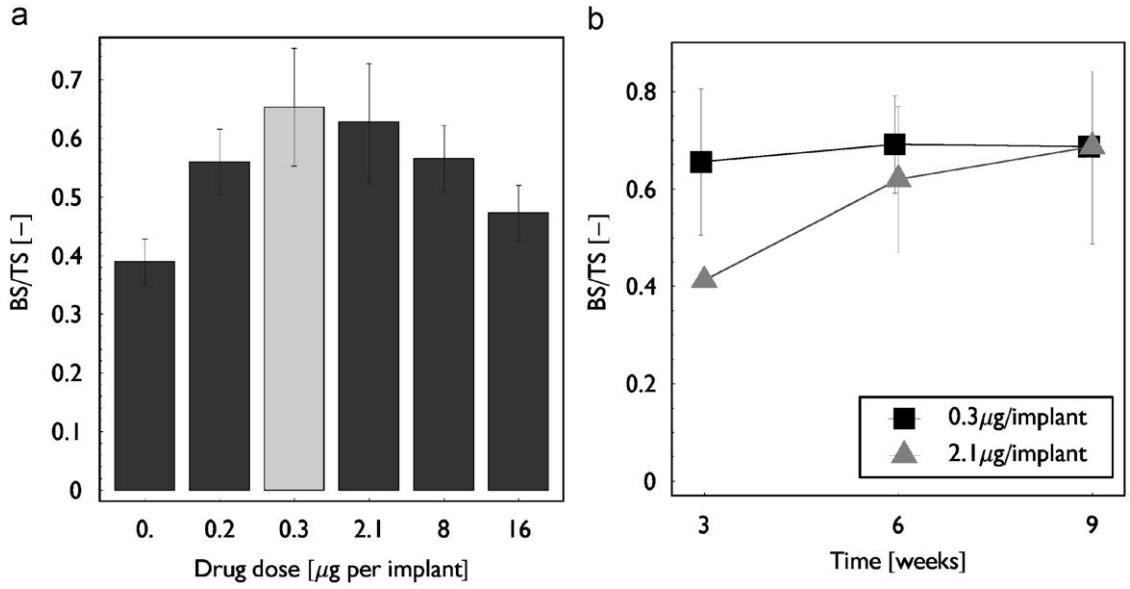

Fig. 3. (a) Mean peri-bone density (BS/TS) in the first 100 μm layer. The dark bars were adapted from (Peter et al.) and the light bar represents the group with 0.3 μg/implant Zoledronate. The mean bone density obtained with the optimal calculated 0.3 μg/implant zoledronate was 4% greater than the highest bone density obtained in our previously published results. (b) Evolution of mean bone density (BS/TS) at 3, 6 and 9 weeks post-op.

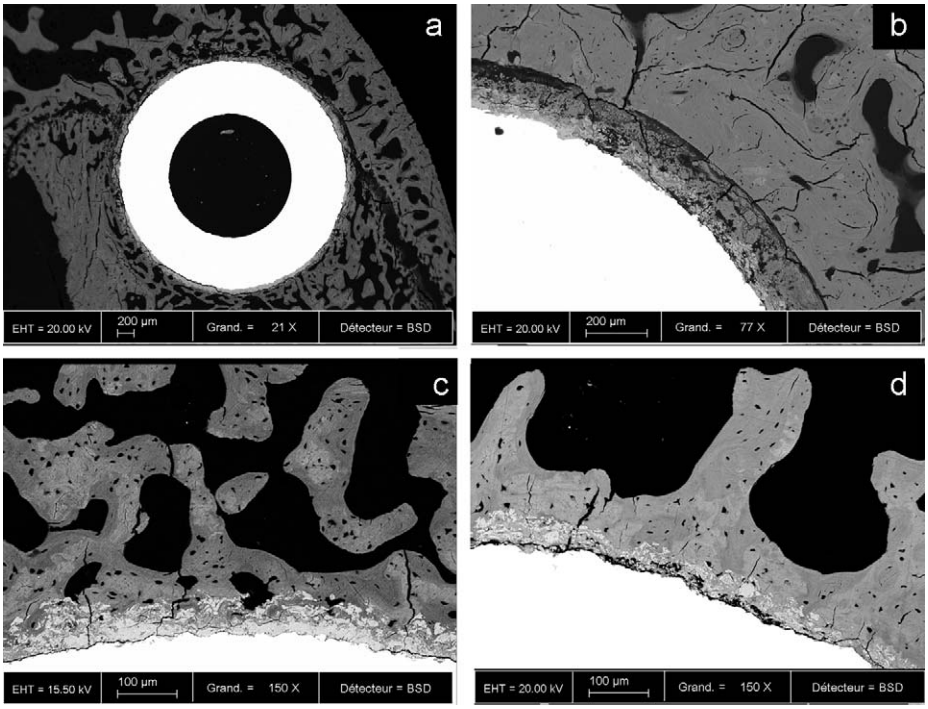

Fig. 4. SEM pictures of implanted condyles: panel (a) shows the bone structure of a condyle implanted with HA-coated implant containing 2.1 µg zoledronate at 3 weeks. The implant integration is qualitatively similar to previously published results. Panel (b) shows a detail of the bone-coating interface at 3 weeks. Bone is not yet entering the coating. Panel (c) shows the interface at 6 weeks with the first signs of coating resorption, and panel (d) shows the interface at 9 weeks with more than 50% of the coating resorbed.

The model presented here is based on several hypotheses which were consistent with the experimental situation addressed. We assumed that the model of a cylindrical implant could be reduced to a one-dimensional geometry. This assumption is relevant in our situation as we analyzed only the average density of a very thin layer of bone and we were not interested in histomorphometry aspects. Moreover, the analyzed slices were not taken from the extremities of the implants, which are in the cortical regions of the condyles.

Fick's law of diffusion for bisphosphonates is certainly a limitation of the model. However, there is a lack of information for the diffusion aspect of bisphophonates in human bone and the use of the experimentally determined effective coefficient of diffusion (Peter, 2004) can be considered as a first approach as an average diffusion behavior is obtained.

We identified from experimental data that the loading function $Y(x)$ increased significantly near the implant surface. This certainly reflects the mechanical stress following press-fit insertion and spring-back effect of bone (Kold et al., 2003). With a different surgical protocol, the stress distribution would certainly be different, and $Y(x)$ would have to be re-calculated.

In the resolution of our model, we simplified the boundary conditions: we set the coating as an infinite source of drug at constant concentration. The relevance of this assumption for short-term studies was confirmed by the SEM observations: at three weeks, the coating was indeed not significantly resorbed. It was probably still protected from osteoclastic resorption by its content in bisphosphonate. This is concordant with the very low release rate of zoledronate by hydroxyapatite (Roussiere et al., 2005). However, this simplifying assumption cannot be used for long-term studies: we observed that the hydroxyapatite coating was partially degraded at 6 weeks, and this degradation continued at 9 weeks. The bisphosphonate concentration in the coating then certainly decreases significantly after 3 weeks. With the second boundary condition, we assumed that the drug concentration is negligible at 2 mm from the implant surface, which corresponds to the growth plate and the bone marrow. Since these tissues are well perfused, the drug is certainly diluted into the blood volume.

The observed degradation of the coating at 6 and 9 weeks, and the lacunae in resorbed areas might reflect the presence of osteocytes in the newly formed bone–implant interface. This is a sign of good implant osteointegration at mid- and long-term post-op with the optimal zoledronate concentration. However, more histology would be needed to confirm this observation.

Our results are certainly dependent on the choice of the drug and on the animal model. In the present study, we determined the drug stimulus function for zoledronate in rats. To extend the model predictions to other active molecules or other animals, the first step would be to determine the drug stimulus function, which we called the drug signature, with the specific drug using the specific animal. To our knowledge, none of the required data for such identification with other animals or with different drugs has been published.

Only a limited number of animals were used in the experimental part of this project. The main objective of this project was to compare the theoretical model's outcomes to an *in vivo* situation. The experiments were therefore designed to validate the model rather than to provide new statistically significant experimental results, which would have required a much larger number of animals.

The principal objective of coating implants with bisphosphonate for local delivery is to increase the fixation of the implant. The pullout force is somehow related to peri-implant bone density (Peter et al., 2005), but other factors, such as bone quality, also have an influence. A mathematical relationship between histomorphometry of bone and its mechanical capacity to resist pullout has yet to be determined (Jakobsen et al., 2006). Thus, the mathematical model presented here only predicts bone density. More work will be needed to link bone density to implant fixation strength.

One of the most important challenges associated to orthopedic implants is to obtain sufficient early fixation to ensure long-term stability, for patients of variable age, daily activity level or bone quality. Although several studies have shown that implants delivering bisphophonate improve this fixation, the bisphosphonate molecule, the dose, or the animal model have always been chosen empirically. So the conclusion of this article is to demonstrate that the theoretical framework presented could be of great interest to predict the bone formation around implant delivering bisphosphonate.

Conflict of interest statement

There is no conflict of interest.

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