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Orthopaedic Implant as Drug Delivery System: a Numerical Approach

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There is a current trend to propose cementless total joint arthroplasty (TJA) to younger patients. These patients have more demanding physical activity resulting in an increased failure rate of the implants. In particular for these type of patients, the desired service life of the implant should be extended. The actual implant used do not fulfil this requirement.

In this study, a new concept of orthopaedic implant is presented where the implant is not only a structural support but also a local drug delivery system. The delivered drug is meant to influence the bone remodeling in a way so as to compensate the effects of peri-implant osteolysis. To test this concept, we extended an existing bone remodeling model to include the effect of a drug. The results show that a more homogeneous bone density distribution can be obtained around the implant. Implants used as drug delivery systems could then be an alternative way to increase implant service life.

Keywords: Drug delivery; Remodeling model; Total hip arthroplasty; Coating; Bisphosphonate

INTRODUCTION

In recent years, cementless implants appeared to be more used in young patients. However, failure rates of hip arthroplasty can exceed 30% after 15 years for patients younger than 50 years old [1]. The long term performance of implants has to be increased.

The main cause of implant failure is loosening following osteolysis caused either by stress shielding [2] or by inflammatory reaction induced by wear particles [3]. Besides the improvement of the material and wear properties of the implant, a new therapy using a systemic treatment with pharmaceutics targeting bone resorption, *e.g.* bisphosphonates [4], has been recently considered. However, the systemic use of drugs presents drawbacks such as important side effects (*e.g.*, throat or stomach ulcers for bisphosphonates [5]) or difficulties in determining the appropriate dosage.

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These difficulties could limit the use of the pharmacological therapy in controlling the peri-implant bone remodeling.

In order to solve those problems, we suggest a new view of the use of implants. The implants would not only be a structural support but also a local drug delivery system. To realise this innovative concept, the stem of a cementless implant could be coated with a carrier (*e.g.*, hydroxyapatite) combined with a drug (*e.g.*, bisphosphonate [6]) which would enable local control of bone remodeling.

In the present study, we numerically investigate the concept of an implant used as a drug delivery system. We modified an existing model developed by our group for calculation of bone density around an implant during remodeling [7]. The effects of drugs were accounted for by locally modifying bone remodeling parameters. We also evaluated the advantage of a partial in comparison to a full stem-biocoating. This last point is motivated by the fact that the peri-implant bone density is uneven. The optimal control of bone remodeling in the implant surrounding could be best achieved by a partial biocoating.

METHODS

Model of Bone Remodeling

Our bone remodeling model [8] takes into account the bone inhomogeneity and bone transverse isotropic symmetry by using two field variables: the relative density ϕ and the anisotropy tensor **M**. To relate the bone adaptation to the mechanical stress environment, the relative density evolution $\dot{\phi}$ is linked to the mechanical stimulus ψ applied to the bone by a piecewise linear evolution relation (Fig. 1). The anisotropy tensor **M** is kept constant with time.

An equilibrium zone, where bone neither resorbs nor densifies is delimited by two threshold stimuli ψ_r and ψ_d. v_r and v_d are respectively the slopes of the resorption and densification rates

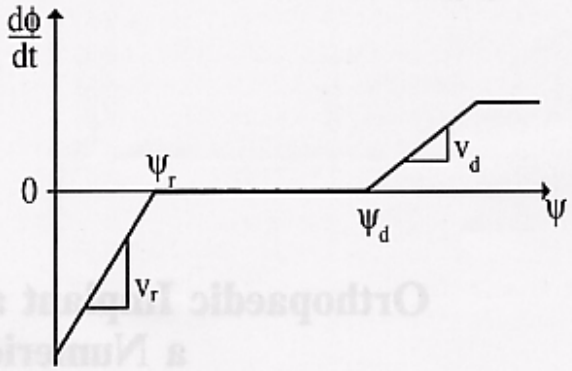

FIGURE 1 Bone relative density evolution in function of mechanical stimulus.

versus ψ. The bone density adaptation function is then determined by the four parameters which are v_r, ψ_r, v_d and ψ_d (Fig. 1). The stimulus ψ was set to a plastic yield stress [8], which is a way of measuring the microdamage, since plastic deformations are needed to create microcracks.

The equation describing the bone adaptation behaviour in our model is [7]:

$$\frac{d\phi}{dt} = \begin{cases} v_r(\psi - \psi_r) & \psi < \psi_r \\ 0 & \psi_r \le \psi \le \psi_d \\ v_d(\psi - \psi_d) & \psi > \psi_d \end{cases} \qquad (1)$$

Model of the Drug Effect

Drugs used to control the disease of bone metabolism, *e.g.* bisphosphonates, affect the bone turnover [6]. This can be modeled by transforming the four main parameters v_r, ψ_r, v_d, and ψ_d in functions depending on the drug effect.

$$v_r(\kappa) = v_r \cdot \kappa \qquad (2)$$

The factor κ is a value between 0 and 1 which is defined for each location in the bone and can be dependent upon the drug concentration or other biological properties. The dependencies for $\psi_r(\kappa)$, $v_d(\kappa)$, and $\psi_d(\kappa)$ are defined in the same way. The implementation of the drug altered relative density evolution ($d\phi/dt$) (Eq. (1)) has been achieved by using a set of parameters $v_r(\kappa)$, $\psi_r(\kappa)$, $v_d(\kappa)$, and

$\psi_d(\kappa)$ calculated with Eq. (2). The dependencies of the parameters $v_r(\kappa)$, $\psi_r(\kappa)$, $v_d(\kappa)$, and $\psi_d(\kappa)$ upon κ will have to be experimentally determined. For the present study, this dependency has been arbitrarily set to a linear relation (Eq. (2)).

Application to Hip Arthroplasty

Geometry and FEM

The three-dimensional geometry of a proximal femur was reconstructed from CT scan slices. The initial bone density distribution corresponds to the density distribution as it has been measured just after implantation of a THR implant. Then, a finite element model of the bone-implant system was obtained with a 3D mesh generator [9]. The FE mesh was based on 8-node isoparametric elements. The evolution equation was iteratively solved by custom-made software REM [7] driving ABAQUS (Hibbitt, Karlsson, & Sorensen Inc., Newpark, USA) analysis program. The forces used to simulate muscle action on the head of the implant have been experimentally determined [10–12].

Global Drug Application

In order to validate the concept of biocoating, three different sets of simulation were used. The parameters were set so as to decrease bone resorption. The first case called Fullcoat 1 was a simulation run with

$$\psi_r(\kappa = 0.5) = \frac{\psi_r}{2}$$

The second one called Fullcoat 2 was a simulation run with

$$v_r(\kappa = 0.5) = \frac{v_r}{2}$$

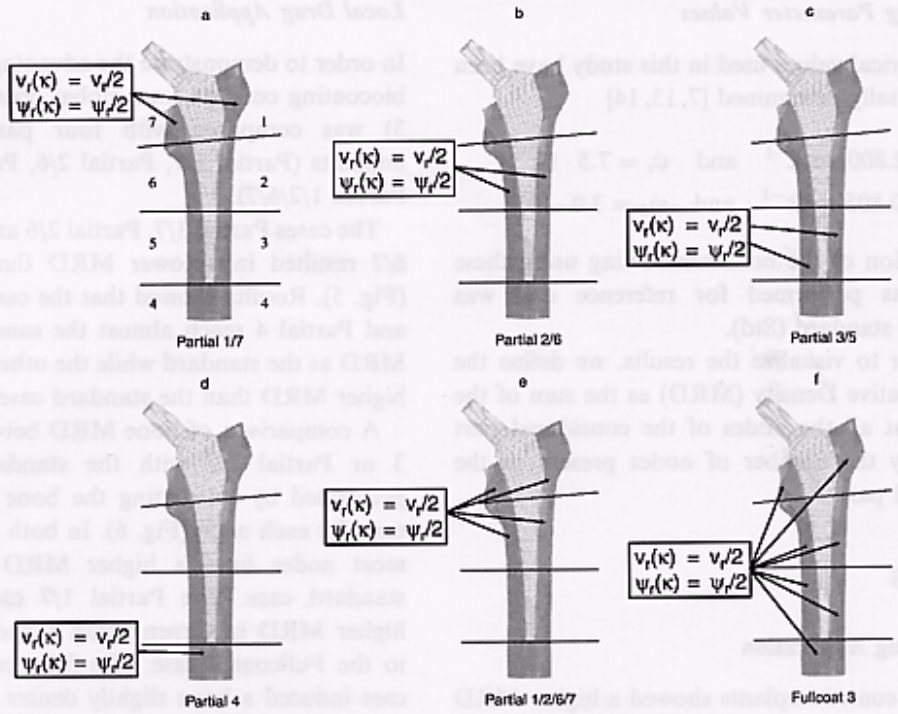

FIGURE 2 Description of the different simulated coatings in reference to the Gruen zones (detailed in a) taken as pairs (1/7, 2/6, 3/5 and 4).

The third one called Fullcoat 3 was a simulation run with

$$\psi_r(\kappa = 0.5) = \frac{\psi_r}{2} \quad \text{and} \quad v_r(\kappa = 0.5) = \frac{v_r}{2}$$

In all three cases, any other parameter was left at the standard values of v_r, ψ_r, v_d, or ψ_d.

Local Drug Application

For the study of local drug effect, $v_r(\kappa)$ and $\psi_r(\kappa)$ were varied at the same time in certain regions of the femur, as shown in Figure 2 and Eq. (3):

$$\psi_r(\kappa = 0.5) = \frac{\psi_r}{2} \quad \text{and} \quad v_r(\kappa = 0.5) = \frac{v_r}{2} \quad (3)$$

The parts of the femur that are not designated by the arrows use the standard values of v_r, ψ_r, v_d, or ψ_d.

Remodeling Parameter Values

The numerical values used in this study have been experimentally determined [7, 13, 14]

$$v_r = 2.800\,\text{week}^{-1} \quad \text{and} \quad \psi_r = 7.5 \cdot 10^{-3}$$
$$v_d = 0.805\,\text{week}^{-1} \quad \text{and} \quad \psi_d = 3.0 \cdot 10^{-2}$$

A simulation of the bone remodeling using these values was performed for reference and was defined as standard (Std).

In order to visualize the results, we define the Mean Relative Density (MRD) as the sum of the densities at all the nodes of the considered part divided by the number of nodes present in the considered part.

RESULTS

Global Drug Application

The three coated implants showed a higher MRD than the standard implant (Fig. 3). The Fullcoat 1 and Fullcoat 3 ended up with higher MRDs than the standard implant, whereas Fullcoat 2 reaches equilibrium with the same MRD than the standard case. All three full coatings needed longer times to reach equilibrium than the standard case corresponding then to a decreased rate of bone turnover. Decreasing ψ_r was more effective to slow down bone resorption than decreasing v_r.

For all Gruen zones and at any time, the MRD was higher in the Fullcoat 3 case compared to the standard (Fig. 4). The most marked differences were located in zones 1 and 7 with a MRD 1.5 time higher than in Std after 50 weeks. The resorption rate ($d\phi/dt$) was 2.2 times higher in the standard case than in the Fullcoat 3 case. When locally observing the MRD evolution (Fig. 4), it was observed that the biggest difference between the standard case and Fullcoat 3 was found in the Gruen zones 1, 2, 6 and 7. The MRD of the zones 3, 4 and 5 was slightly higher in the Fullcoat 3 case than in the standard case.

Local Drug Application

In order to demonstrate the advantage of a partial biocoating concept, one global coating (Fullcoat 3) was compared with four partially coated implants (Partial 1/7, Partial 2/6, Partial 3/5 and Partial 1/2/6/7).

The cases Partial 1/7, Partial 2/6 and Partial 1/2/6/7 resulted in a lower MRD than Fullcoat 3 (Fig. 5). Results showed that the cases Partial 3/5 and Partial 4 reach almost the same equilibrium MRD as the standard while the other three keep a higher MRD than the standard case.

A comparison of bone MRD between Fullcoat 3 or Partial 1/7 with the standard case was performed by calculating the bone MRD difference for each node (Fig. 6). In both coating cases, most nodes have a higher MRD than in the standard case. The Partial 1/7 case reached a higher MRD in Gruen zones 1 and 7 compared to the Fullcoat 3 case. The fully coated implant case induced a bone slightly denser in the medial proximal bone next to the implant and in the lateral proximal outer region of the bone. The

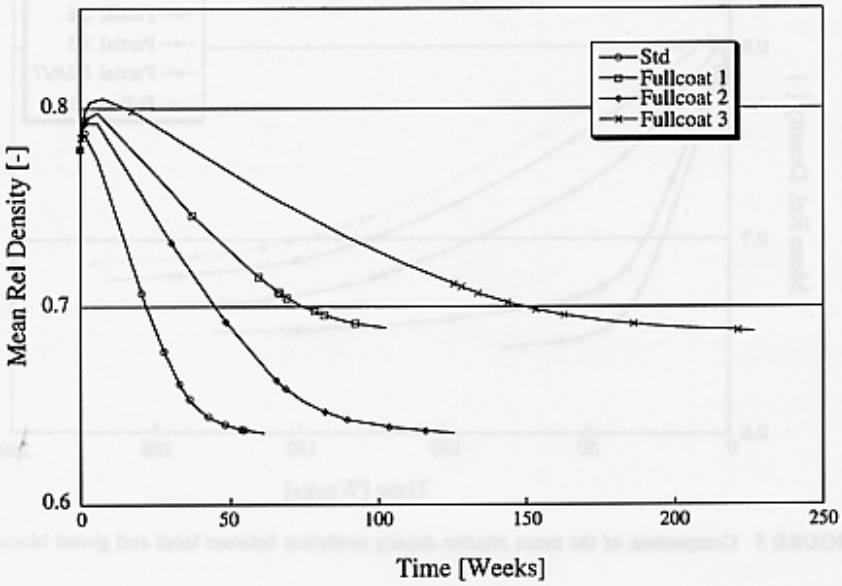

FIGURE 3 Evolution of the mean relative density in time for four cases being Standard (Std), 50% decreased ψ_r (Fullcoat 1), 50% decreased v_r (Fullcoat 2), 50% decreased ψ_r and v_r (Fullcoat 3).

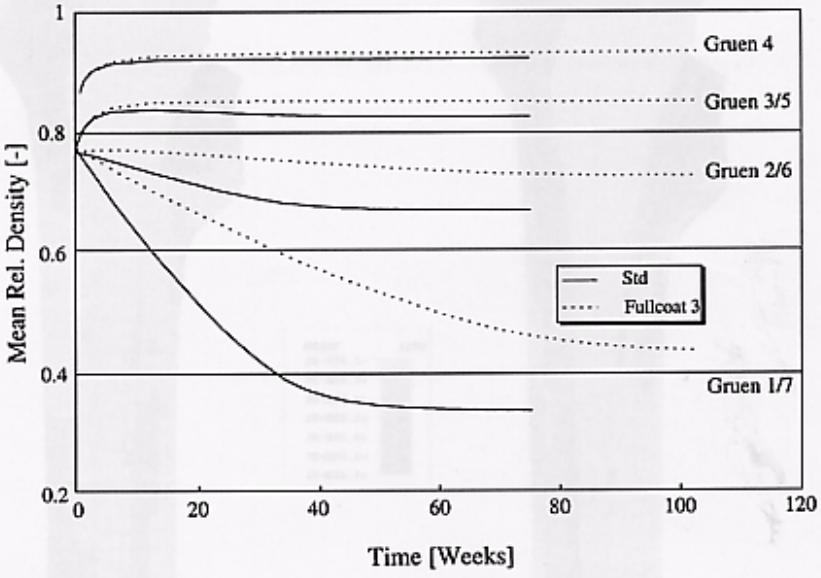

FIGURE 4 Comparison of the mean relative density evolution between the Std and Fullcoat 3.

main difference resided in the zones 2 and 6, in particular in the lateral region next to the implant, where the bone around the full coating case is 10% denser as in Partial 1/7. In the regions 3/5 and 4, the fully coated implant resulted also in a denser bone as compared to a

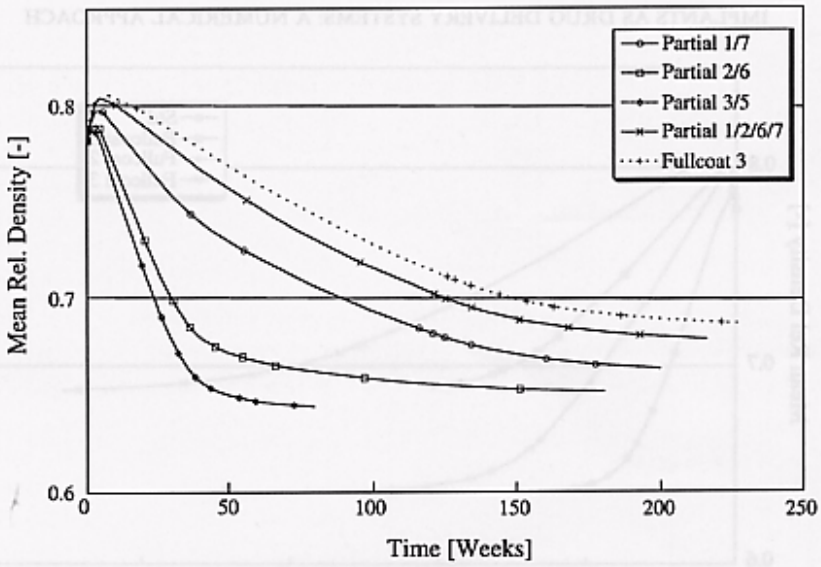

FIGURE 5 Comparison of the mean relative density evolution between local and global biocoating.

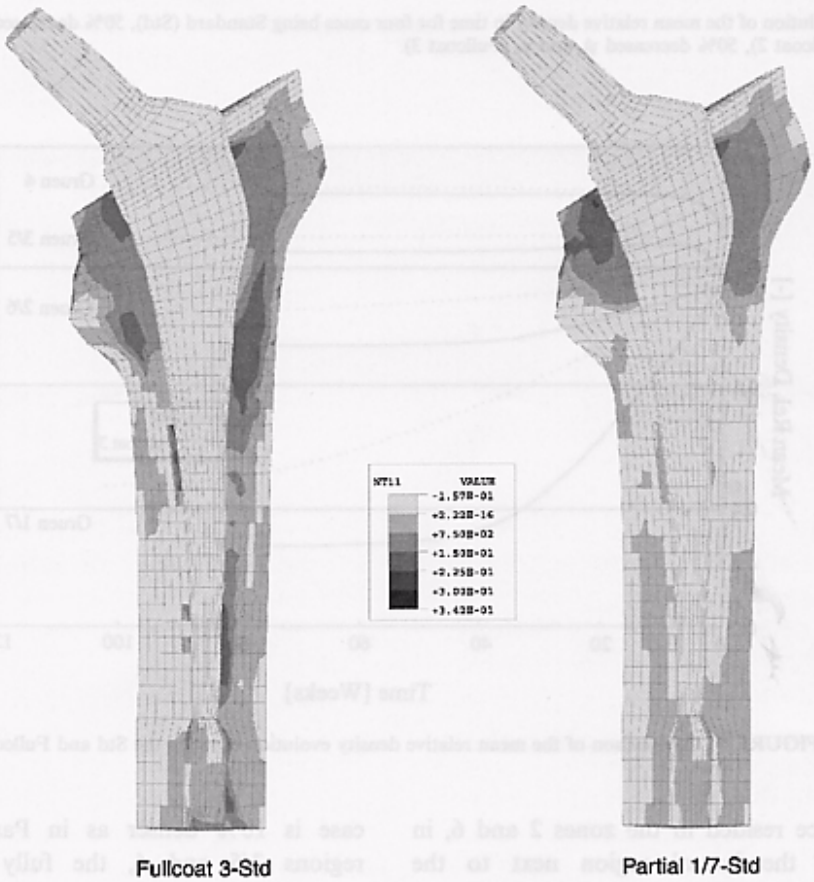

FIGURE 6 Spatial MRD variation of Full coating and Partial coating compared to Std. Dark zone represents the highest difference in bone MRD while clear zone represents slight difference.

partial coating. In all cases, the denser bone was mainly located in lateral part and the higher increases were next to the implant.

DISCUSSION

There is a need to increase the life span of hip implants especially for younger patients. To this end, Shanbhag [4] studied the inhibition of wear debris mediated osteolysis in a canine total hip arthroplasty model by oral use of a bisphosphonate (alendronate sodium). Despite promising results, the systemic use of bisphosphonates bears some dangers like throat damage or ulcer [5]. Therefore we propose to coat the implant with a drug as bisphosphonate to create a local delivery system. This allows to control the bone remodeling around the implant. The basic underlying assumption is that decreasing the bone resorption in the early stage following a TJA could considerably increase the stability of the implant resulting in a longer implant service life. In the present study, we tested this hypothesis by extending a bone remodeling model for analysing the effect of a drug coated on the implant surface.

The decrease of the two resorption parameters of the model ψ_r and v_r were effective in increasing the bone mean relative density around the implant. However only the variation of ψ_r enables maintenance of higher MRD up to the equilibrium state. The influence of decreased v_r lies mainly in delaying bone resorption. For example, in order to reach a MRD $\phi = 0.65$, it took 40 weeks with a standard implant, 75 weeks with a decreased v_r (Fullcoat 2) while for the two cases Fullcoat 1 (ψ_r decreased) and Fullcoat 3 (ψ_r and v_r decreased) the MRD stayed always above 0.65 (Fig. 3).

By comparing the evolution of the mean MRD (Fig. 3), for the couples Std-Fullcoat 2 and Fullcoat 1-Fullcoat 3, the observed effect of a decreased v_r is to increase the time to reach the equilibrium MRD. The consequence of this is that at the same moment in the remodeling process (for example week 50), the coating inducing a decreased v_r generated a bone of higher MRD around the implant. This leads to the conclusion that the ideal drug would be one that decreases ψ_r in order to reach a higher equilibrium MRD and decreases v_r in order to reach the equilibrium by keeping the highest possible MRD during the remodeling process.

The distal part of the implanted femur tends to increase its MRD with time (Fig. 4) which has been associated to the stress-shielding problem [15]. In the Fullcoat as in the Partial cases, the model indicated that the distal parts of the implanted bone (zones 3, 4 and 5) were denser than in the initial case whereas the proximal part of the bone (zone 1, 2, 6 and 7) resorbed. This leads to a situation which is biomechanically unfavourable to the stability of the bone-implant system [16]. Those observations lead to the concept of partial biocoating.

Since the densification of the distal zones (3, 4 and 5) is not desirable, partial coatings were simulated successively in the zones (1, 7) and (2, 6) and (1, 2, 6 and 7). Interestingly, in all three partial coatings, the MRD in the modified zone was higher than in the same zone for the full biocoating. This result favoured the use of a local coating compared to a full coating for the two reasons that first a higher bone density is obtained in the needed regions and second no decrease of bone resorption is induced in the distal part of the implant where an over densification already took place.

Two clinical studies related the use of partially coated implants. McAuley [17] showed that in the case of an anatomical medullary locking hip implant, the full coating results in less bone loss in the proximal femur but a density increase in the distal part of the femur. But the authors admit themselves that those results are probably particular to the design of this implant. Rosenthall [18] compared the density evolution in all Gruen regions around Multilock implants where, some were proximally coated with hydroxyapatite while the others were not coated. They could show that in any Gruen zone and at almost

any moment, the density was higher in the proximally coated implant. These two studies illustrate the conflicting results that can be obtained *in vivo*. This fact highlights the usefulness of a numerical model to estimate the influence of different implants on the peri-implant bone remodeling.

The model used constant values to simulate the effect of the drug. The decrease of drug activity over time or the diffusion of drug in the bone were not accounted for. These effects could modify the calculated bone MRD. The diffusion of the drug in the bone will be measured in an experimental study and incorporated in the developed model. Regarding the decrease of drug activity, this effect is less important for bisphosphonate as it has been shown that this drug is not degraded during its stay in the body [6].

CONCLUSION

In the first part of this work, we showed that the new implant concept is able to modify the equilibrium bone MRD. By decreasing the resorption parameters, we observed a higher MRD distribution and a different bone turnover compared as to the standard case. By using the developed model, the effect of modifying bone remodeling parameters could be estimated which brought useful information for specifying the targeting for future drugs used in controlling the bone remodeling.

In the second part, simulation of a partial biocoating resulted in a MRD distribution which was biomechanically more favorable for a longer service time than the one obtained for a full coating. Therefore the concept of partial biocoating could be a promising technique to improve the service life of implants and could be particularly useful for young patients with cementless implant.

Finally, the presented model was able to take into account the action of bone turnover-modifying drugs and to furnish suggestions for the choice of drug which would provide the ideal peri-implant bone density distribution.

Acknowledgements

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