Medical Engineering and Physics 107 (2022) 103859

Contents lists available at ScienceDirect

Medical Engineering and Physics

journal homepage: www.elsevier.com/locate/medengphy

A comparison between the effect of systemic and coated drug delivery in osteoporotic bone after dental implantation

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ARTICLE INFO

Keywords:
Bone remodeling
Systemic drug delivery
Local drug delivery
Zoledronate
Finite element method

ABSTRACT

The increased life expectancy has boomed the demand of dental implants in the elderly. As a consequence, considering the effect of poorer bone quality, due to aging or associated diseases such as osteoporosis, on the success of dental restoration is becoming increasingly important. Bisphosphonates are one of the most used drugs to overcome the effect of osteoporosis as they increase bone density. Bisphosphonates modify the physiological bone remodeling process by adhering to the bone surface, reducing the activity of osteoclasts. This study aims at comparing the effect on bone remodeling of two drug delivery methods of Bisphosphonates: local delivery by coating the implant surface and systemic delivery. A chemo-mechano-biological bone remodeling model validated in a previous paper was used here. The two drug delivery schemes were modeled by means of a finite element approach. In the systemic drug delivery case, the amount of drug that reaches the bone compartment was calculated using a pharmacokinetic model while in the local drug delivery system, the dose was calculated using Fickean diffusion. In particular, the effect of Zoledronate is studied here. The two drug delivery approaches are compared between them and with a control case with no drug. The results show that the use of Bisphosphonates increases the mechanical strength of bone, thus improving the implant fixation along time. Systemic drug delivery affects the entire skeleton, while local drug delivery only affects the area around the dental implant, which reduces the side effects of Bisphosphonates, such as increasing the mineral content, which may promote bone brittleness and microdamage far from the implant. These results support the conclusion that dental implants coated with Bisphosphonates can be a good solution for osteoporotic or low bone density patients without the long-term side effects of systemic drug delivery.

1. Introduction

Osteoporosis is a skeletal disease that results in a decrease in bone mass and destruction of bone tissue, leading finally to bone brittleness with a higher risk to fracture [1,2]. On the other hand, osteopenia is defined as a physiological period in which the mineral density reduces from 10% to 25%, being usually a precursor to osteoporosis [3]. This phenomenon has been associated with various factors, such as Calcium and vitamin D deficiencies, sedentary lifestyle, genetic factors, and postmenopausal estrogen deficiency [4,5].

The demand for dental implants among patients with osteoporosis is rapidly growing [6]. Elders are subjected to partial or complete edentulous conditions related to natural aging and related diseases. As an immediate consequence, the demand of dental implants is expected to increase among this population that many times suffer from chronic diseases such as osteoporosis, which may compromise the success of dental implantation. Some authors have suggested that the success of a dental implant may be severely impaired in a patient with osteoporosis or osteopenia [7].

Bone growth around an implant is a continuous cyclic process controlled by the homeostatic competition between osteoclasts and osteoblasts. Implants that secrete growth factors have been shown to stimulate bone formation [8]. In particular, implants that secrete Bisphosphonate reduce bone resorption and improve the implant fixation [9]. However, recently several reports have been published showing that Bisphosphonates may provoke osteonecrosis of the mandible after

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https://doi.org/10.1016/j.medengphy.2022.103859
Received 19 January 2022; Received in revised form 21 July 2022; Accepted 22 July 2022
Available online 23 July 2022

both oral or intravenous treatments [10]. The systematic use of Bisphosphonates has other side effects such as fever, sore throat, and ulcer production, reducing the efficacy of the treatment [11,12]. Therefore, other methods are being considered to minimize these side effects. For example, injecting alendronate as a gel into the implant site [13], injecting zoledronic acid into the bone chamber, [14] using nanotubes containing zoledronic acid in the implant [15], or using a layer of fibronectin with the addition of pamidronate and Ibandronate [16] are some possible alternatives methods to deliver Bisphosphonates.

Some studies have confirmed the positive impact of the systemic use of Bisphosphonates on the bone density around dental implants [10,17, 18]. However, Bisphosphonates should not invade the skeletal system as a whole to avoid the side effects mentioned above, so the target should be only the tissue directly surrounding the implant. The quality of this neighbor tissue is essential in promoting primary fixation of the implant, which is an essential factor in its long-term stability since excessive micromotions at the bone-implant interface may activate osteoclasts, increasing bone resorption and decreasing bone osseointegration, which may lead to long-term implantation failure.

In a previous study [19], we examined the effect of systemic medication on bone remodeling around implants. However, a similar study with local drug delivery does not exist in the literature, at least up to the authors' knowledge. In this work, we analyze the effects of Bisphosphonate when coated to implants to avoid the adverse effects of systemic drug delivery and compare such effects with those of systemic drug delivery. The present model considers the activity of the cells involved in bone remodeling and the chemical interactions in the RANK/RANK-L/OPG pathway, as well as the diffusion of the drug into bone and how the drug concentration affects the physiological activity. This multiphysics model is solved by means of the finite element method, which allows to compare the effect of different drug doses in systemic and local drug delivery after implant fixation.

2. Materials and methods

A mandibular finite element model was developed with teeth and periodontal ligaments (PDLs) that also included an implant placed in the location of the first right molar. The specific steps for designing the dental implant are described in [20] while the finite element model and corresponding boundary conditions are specified in [19], where additional details can be found. The FE model was created in ABAQUS (ABAQUS 6.11, Dassault Systmes, Vlizy-Villacoublay, France), including the right premolar, second right molar, corresponding periodontal ligaments, implant, dental crown, and mandibular bone. Fully bonded condition was considered between the bone and dental implant surfaces.

The phenomenological model of bone remodeling [21] also described in [19] was used to obtain the initial density distribution. Briefly, the boundary conditions were established by applying the muscle reaction forces during a chewing cycle, while the nodal displacements of a set of nodes located at the surface of the mandible condyles were appropriately restrained. Depending on the teeth involved in chewing, the role of the muscle forces and the corresponding support conditions of the joints will vary [22,23]. After obtaining the initial density distribution and the displacements resulting in such a physiological situation, and with the objective of reducing the computational cost, a section of the mandible, as depicted in Fig. 1a, c, was separated. The boundary conditions, corresponding to the displacements resulting from the whole mandible resolution with the implant, were applied to the mesial and distal surfaces of this cut section to perform the simulations.

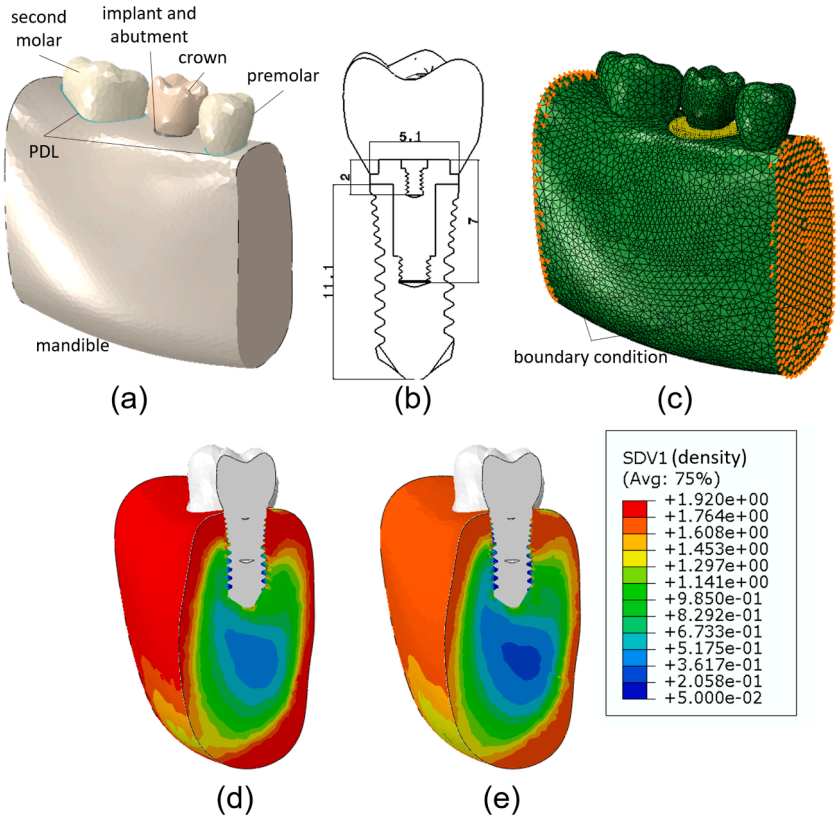

Fig. 1. (a) Isolated section of the mandible containing the right premolar with its PDL, the dental implant, the right first molar and its PDL, (b) cross section of the dental implant used (dimensions in mm), (c) finite element mesh of the isolated part with the boundary conditions, (d) density distribution in a labial-lingual cut view of the isolated part, and (e) density distribution of the same cut view for the osteoporotic state.

Also, the density values obtained in the cut section (Fig. 1d) were reduced in such a way that a reduction in the modulus of elasticity of 33% ($\rho > 1.2\ g/cc$) in cortical bone and of 66% ($\rho < 1.2\ g/cc$) in trabecular bone were obtained, which correspond to standard reductions for osteoporotic patients [24]. Fig. 1e shows the corresponding density distribution after such reduction.

Bone density changes due to the cyclic mechanical stimulation induced by mastication. Therefore, to analyze the effect of the drug, a control case without any drug provision and only mechanical stimulation was used. Two types of drug administrations were considered and denoted as systemic (SDD) and local drug delivery (LDD). 2, 5, and 10 mg of drug dose were used for the SDD conditions and for different time intervals of 90, 180, and 360 days of drug administration. In the case of LDD, 2, 5, and 10 $\mu g/mm^3$ of drug were established.

2.1. Interaction between osteoclasts and osteoblasts

In this study, a mathematical model of interaction between osteoclasts and osteoblasts based on previous studies [19,25] was used. Briefly, this model considers the RANK/RANK-L/OPG pathway that regulates the differentiation process of osteoclasts and osteoblasts that happens during bone remodeling. The biochemical interaction between these biochemical substances and cells is described in a continuous context by means of a set of differential equations that controls their concentrations and those of cells. The cellular interaction is mediated by the activation of cellular receptors. These receptors may bind to molecules secreted by other cell types, to molecules secreted by the same cell type, or to other transmembrane molecules by cell-to-cell contact. Fig. 2 represents the interactions involved in bone remodeling as well as the mechanical environment influence on osteoblast and osteoclast activity. The different cell types presented in this model respond to the activation of their receptors by creating new molecules or by differentiating to other cell phenotypes or dying. The equations used model the concentrations of responsive osteoblasts (B_r), active osteoblasts (B_a), and active osteoclasts C, and may be stated as (for more details refer to [19,25]):

$$\begin{aligned}
\frac{dB_r}{dt} &= D_R\pi_{TGF_\beta} - \frac{D_B}{\pi_{TGF_\beta}}B_r \\
\frac{dB_a}{dt} &= \frac{D_B}{\pi_{TGF_\beta}}B_r - k_B B_a \\
\frac{dC}{dt} &= D_C\pi_{RANK-L} - D_A\pi_{TGF_\beta}C, \\
\frac{dv_b}{dt} &= k_{form}B_a - k_{res}C
\end{aligned} \tag{1}$$

where π_{TGF_β} and π_{RANK-L} represent the fraction occupied by the TGF_β and RANK receptors, D_R is the pre-osteoclast differentiation rate, D_B stands for the responsive osteoblast differentiation rate, k_B is the active osteoblast death rate, D_C is the advanced osteoclast differentiation rate, and D_A is the osteoclast apoptosis rate by TGF_β. The bone formation and resorption rates per cell are denoted as k_{form} and k_{res}, respectively.

To study the effect of systemic drug delivery (SDD) on bone remodeling, it is necessary to use a pharmacokinetic model to obtain the concentration of the drug in the bone chamber. Here, the model presented in [26] was used to study the pharmacokinetics of Zoledronate. This model states as follows:

$$\frac{dA}{dt} = -KD \times A \tag{2}$$

where A is the drug amount in the effect site, and KD represents the first-order constant decay rate. The difference between the pharmacokinetic model used in this study and the previous one in [19] refers only to the number of chambers used. In our previous study, to analyze the systemic effect of Ibandronate on bone remodeling, a 4-chamber model was used, while here, we used a 1-chamber model.

On the other hand, when studying the drug's local effect (LDD) on bone remodeling, since the drug diffuses directly into the bone chamber, there is no need for using any pharmacokinetic model, since the concentration of the drug (c_d) can be calculated by means of the Fick's law for diffusion [27]:

$$\frac{\partial c_d}{\partial t} = \nabla(D\nabla c_d) \tag{3}$$

where D is the effective coefficient of diffusion of Zoledronate into bone

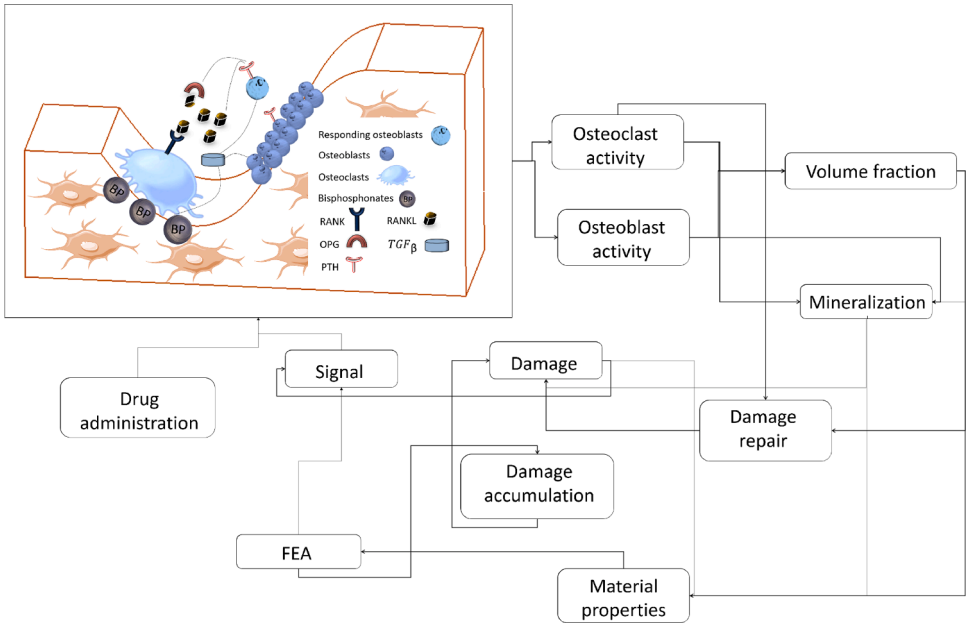

Fig. 2. Schematic representation of the bone remodeling model showing the interaction between bone cells, external forces and the effect of Bisphosphonates on osteoclasts activity.

marrow which is 800 $\mu m^2/day$ [27].

Zoledronate, like other Bisphosphonates, binds to bone minerals and inhibits osteoclast activity [28]. According to this, in the Eq. (1), that defines the osteoclast concentration is modified as follows [29]:

$$\frac{dC}{dt} = D_C\pi_{RANK-L}(1 - EFF) - D_A\pi_{TGF_\beta}C$$
$$EFF = \begin{cases} \dfrac{(KD \times A)^{nH}}{EKD_{50}^{nH} + (KD \times A)^{nH}} & \text{SDD} \\ \dfrac{I_{\max} c_d^{nH}}{IC_{50}^{nH} + c_d^{nH}} & \text{LDD} \end{cases} \quad (4)$$

with EKD_{50} the value of $KD \times C_d$ that leads to 50% of inhibition, $I_{\max}$ the maximum inhibition fraction that has been here considered as equal to one [30], IC_{50} the concentration that produces 50% of the maximum inhibition that was fixed here to 3 nM [31], and nH is the Hill's coefficient. A and c_d are the amount of Zoledronate in the bone chamber which are calculated with Eqs. (2), and (3) respectively.

2.2. Effect of minerals on damage

When bone is formed, the new tissue is mainly made of collagen. Mineralization consists of rapid stages that take several days to reach 60% of the maximum amount of minerals and a slow stage that takes several years [32,33]. The evolution of the ash fraction in the second stage of mineralization is obtained by:

$$\alpha(t) = \alpha_{\max} + (\alpha_0 - \alpha_{\max})e^{-\kappa t} \quad (5)$$

where $\alpha(t)$ represents the ash fraction at time t, that is, the fraction of mineral volume per unit dry bone volume, $\alpha_{\max}$ and α_0 are the maximum and initial amount of ash fraction, respectively, and κ is the mineralization constant. As the first stage of mineralization is fast in terms of the representative time of bone remodeling, as in other works [32,33], it will not be considered in our simulations.

The evolution of damage ($\dot{d}$) results from the rate of accumulation ($\dot{d}_{acc}$) and repair ($\dot{d}_{rep}$) of these microcracks inside bone, so its evolution can be defined as follows:

$$\dot{d} = \dot{d}_{acc} - \dot{d}_{rep} \quad (6)$$

Damage accumulation is produced both under tension and under compression, being a function of the applied strain and the number of cycles. In contrast, damage repair depends on the velocity of bone resorption since this bone removal simultaneously removes damage. So, d_{rep} may be related to $\frac{dv_b}{dt}$ as defined in [19,20,25].

Increasing the amount of Calcium is associated with the ash fraction ($[Ca] = \frac{259.2}{0.65}\alpha$ [34]) and reduces the lifespan of fatigue (N_f) as demonstrated by Martinez-Reina et al. [33], so we can write [19]:

$$N_f = \frac{K_i}{\varepsilon^{\delta_i}}, i = c(compression), t(tension)$$
$$K_t([Ca]) = 10^7\left(\frac{\varepsilon_u([Ca])}{\beta}\right)^{\delta_t} \quad (7)$$

where ε is the strain level, and δ_i and β are constants. ε_u is the ultimate strain that may be experimentally related to the Calcium concentration as [33]:

$$log\varepsilon_u = 25.425 - 11.341log[Ca] \quad (8)$$

After obtaining the initial density distribution using the Stanford bone remodeling model, the simulations were performed using the chemo-biological-mechanical bone remodeling model coupled with the pharmacokinetics model, as briefly described above. Besides the concentration of the different biochemical substances and of the cells involved in bone remodeling, the bone volume fraction, the level of mineralization and the local damage were obtained from that model, and from them, the bone elastic modulus was computed pointwise as detailed in [19].

3. Results

The results of the bone remodeling simulation for the control, for the systemic case after several periods of 180 days of drug administration, and for different doses of coated Zoledronate on the implant surface are depicted in Figs. 3–5. Fig. 3a shows the bone volume fraction distribution obtained after solving the physiological case using the phenomenological Stanford bone remodeling model [21] under mastication conditions, and after considering the reduction in bone mass density in trabecular and cortical bone for patients with osteoporosis, as described above. This bone volume fraction distribution was used as the initial condition in the subsequent simulations of the control, SDD, and LDD cases. As can be seen in this figure, the outer surfaces of the bone are denser (cortical bone), while the most interior regions are lighter (spongy bone).

Figs. 3 –5 show the results for simulation times of 360 and 720 for the control case and for different types of drug delivery and drug doses. The results show an increase in the volume fraction, in the ash fraction (mineral content) and in damage when increasing the drug doses for both SDD and LDD. This increase in bone volume fraction after 720 days was 0.78 for the control case, while this quantity raised up to its maximum value for all drug cases. Such an increase in the volume fraction is evident in the regions of the root and crest of the implant. However, the bone volume fraction in these regions is lower than in the other areas in the control case. Comparing the results for times of 360 and 720 days, it is clear that these values increase with time. Those figures also show that local drug delivery affects only the bone around the coated implant, while SDD affects the entire mandible.

The ash fraction in the trabecular bone around the implant threads resulted the lowest in the control case (Fig. 4b-c). The same trend is observed for low systemic doses of the drug (Fig. 4d-g). When increasing the SDD dose, the ash fraction increases in these regions and in the rest of trabecular bone. In that same region, the ash fraction also increases when increasing the dose in the LDD (Fig. 4j-o). However, this increase in the ash fraction during LDD is only observed in the bone around the implant. The maximum amount of ash fraction increase in this region with respect to the control case, was of 64% for 10 mg SDD and of 80% for 10 $\mu g/mm^3$ LDD.

Fig. 5 shows the damage distribution around the implant. Since fixing the upper and lower limits of the legends in Figs. 4 and 5, prevents to observe the small differences between the different times and doses unlike in Fig. 3, we used different limits in the legends in such figures for an easier interpretation. The amount of damage in the control case is more significant in cortical than in trabecular bone, and as shown in Fig. 10, the damage tends to a constant value in the long term. Increasing the dose in the SDD case increases the amount of damage in trabecular bone, as shown in Fig. 5i. In the case of local drug delivery, the amount of damage in the bone around the implant is more significant (Fig. 5j–o), and may reach its maximum value when increasing the drug dose.

The temporal changes for the volumetric averaged values of bone

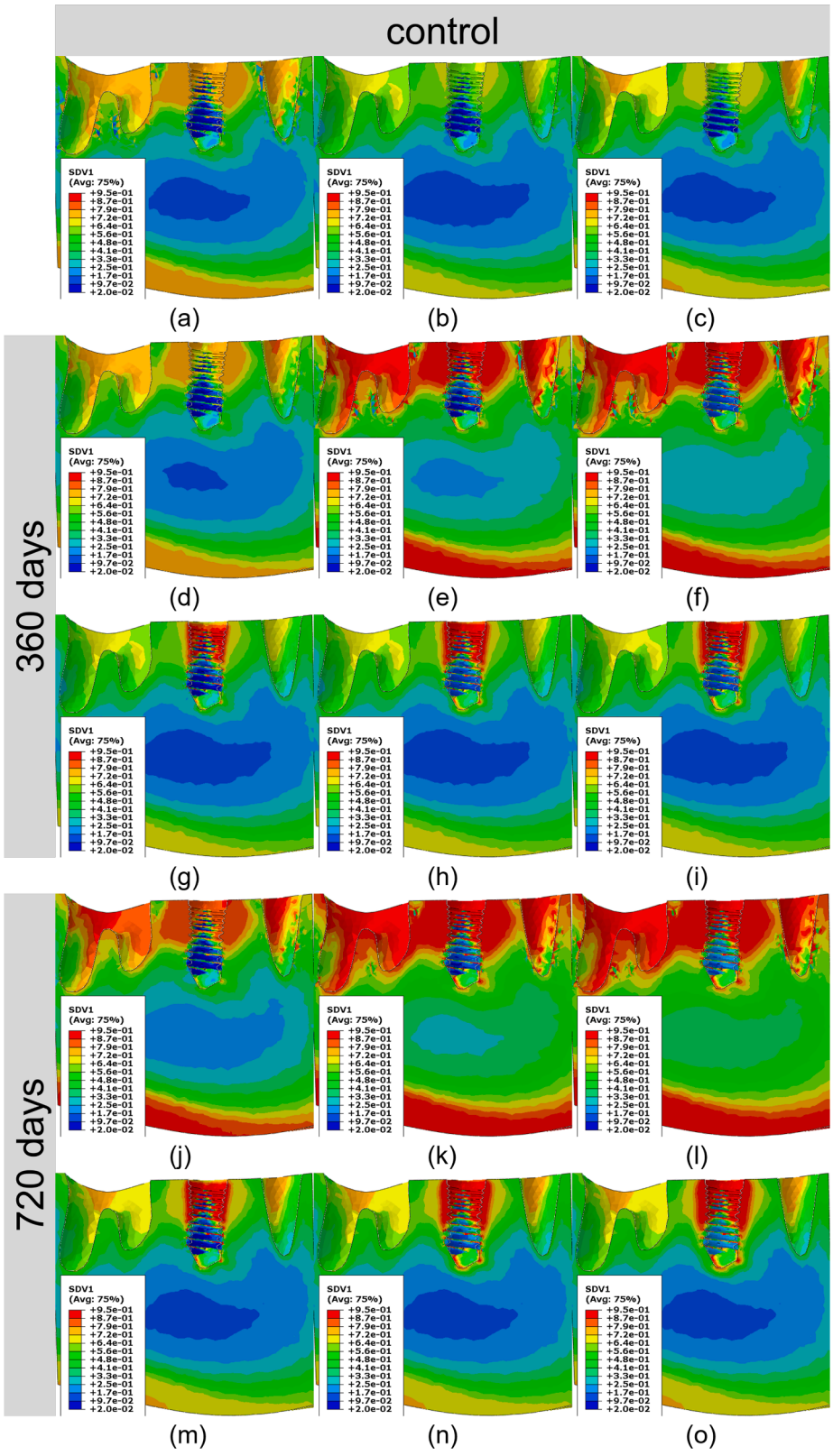

Fig. 3. Bone volume fraction distribution in the control case, SDD with drug administration in periods of 180 days, and LDD. (a) initial condition for all simulations, (b) control case after 360 days of simulation, (c) control case after 720 days of simulation. Different doses of Zoledronade administration in SDD every 180 days and LDD after 360 days of simulation: (d) 2 mg, (e) 5 mg, (f) 10 mg in SDD, (g) 2 $\mu g/mm^3$, (h) 5 $\mu g/mm^3$, (i) 10 $\mu g/mm^3$ in LDD, and after 720 days of simulation: (j) 2 mg, (k) 5 mg, (l) 10 mg in SDD, (m) 2 $\mu g/mm^3$, (n) 5 $\mu g/mm^3$, (o) 10 $\mu g/mm^3$ in LDD.

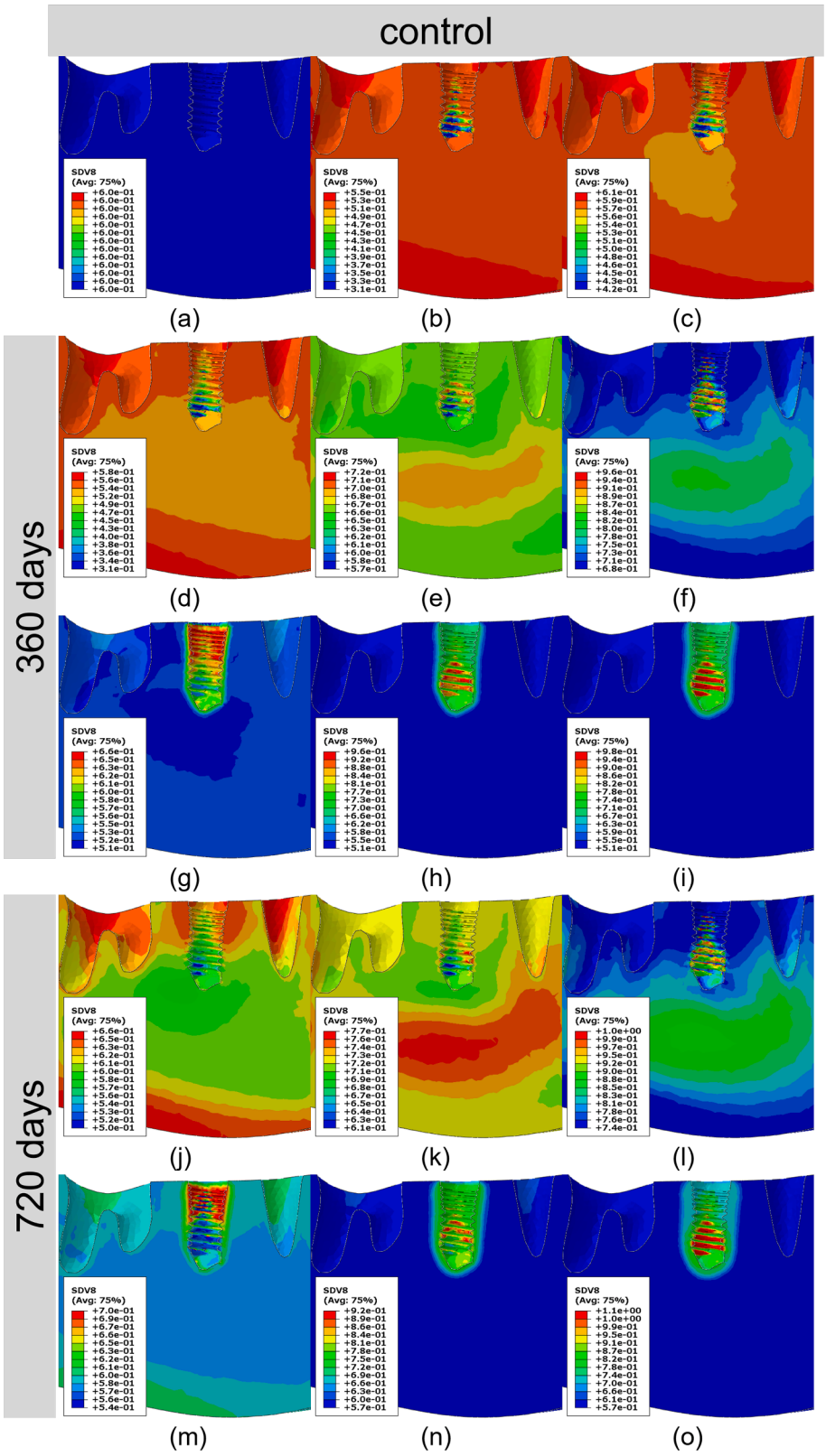

Fig. 4. Ash fraction distribution in the control case, SDD with drug administration in periods of 180 days, and LDD. (a) initial condition for all simulations, (b) control case after 360 days of simulation, (c) control case after 720 days of simulation. Different doses of Zoledronade administration in SDD every 180 days and LDD after 360 days of simulation: (d) 2 mg, (e) 5 mg, (f) 10 mg in SDD, (g) 2 $\mu g/mm^3$, (h) 5 $\mu g/mm^3$, (i) 10 $\mu g/mm^3$ in LDD, and after 720 days of simulation: (j) 2 mg, (k) 5 mg, (l) 10 mg in SDD, (m) 2 $\mu g/mm^3$, (n) 5 $\mu g/mm^3$, (o) 10 $\mu g/mm^3$ in LDD.

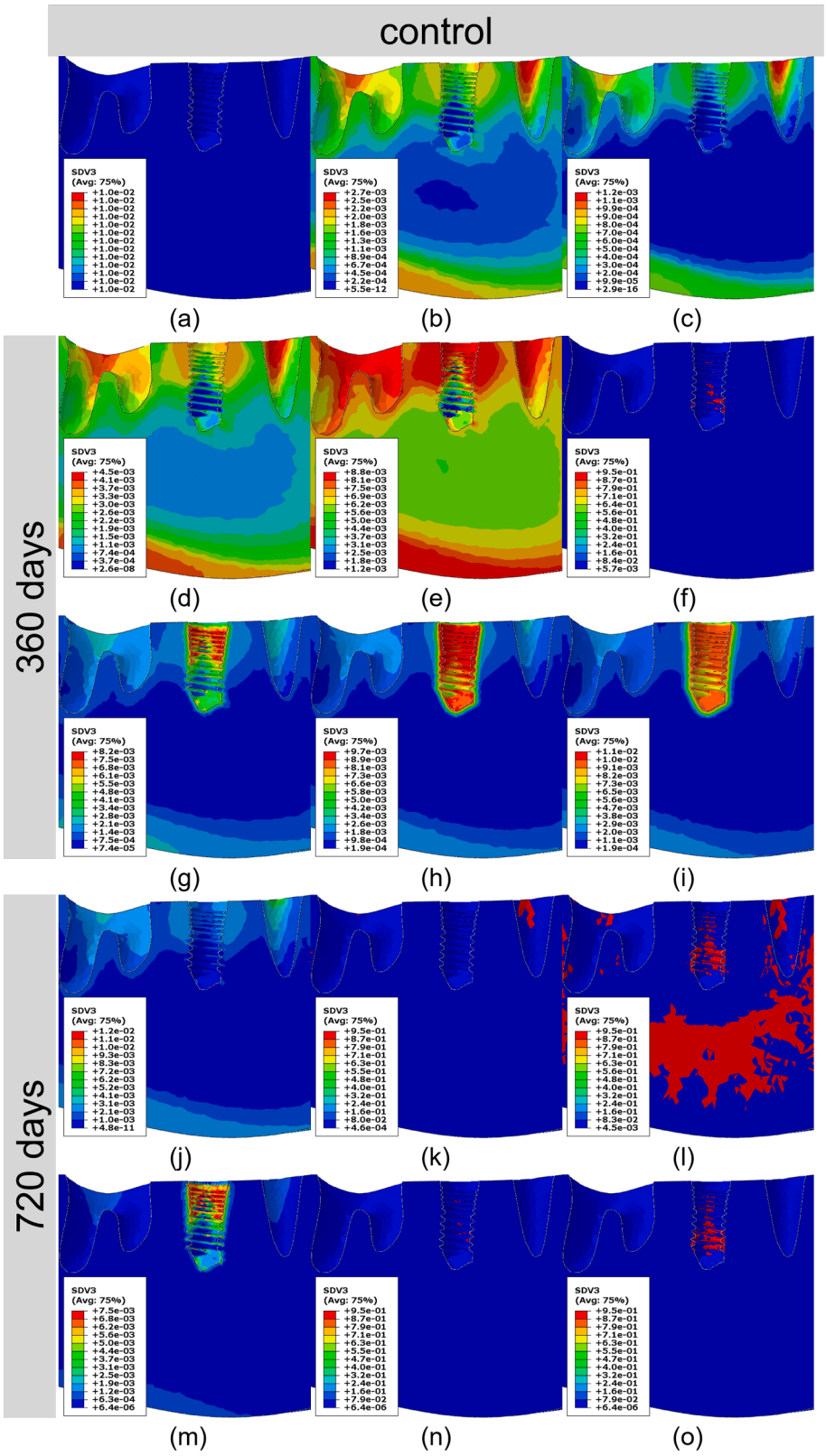

Fig. 5. Damage distribution in the control case, SDD with drug administration in periods of 180 days, and LDD. (a) initial condition for all simulations, (b) control case after 360 days of simulation, (c) control case after 720 days of simulation. Different doses of Zoledronade administration in SDD every 180 days and LDD after 360 days of simulation: (d) 2 mg, (e) 5 mg, (f) 10 mg in SDD, (g) 2 $\mu g/mm^3$, (h) 5 $\mu g/mm^3$, (i) 10 $\mu g/mm^3$ in LDD, and after 720 days of simulation: (j) 2 mg, (k) 5 mg, (l) 10 mg in SDD, (m) 2 $\mu g/mm^3$, (n) 5 $\mu g/mm^3$, (o) 10 $\mu g/mm^3$ in LDD.

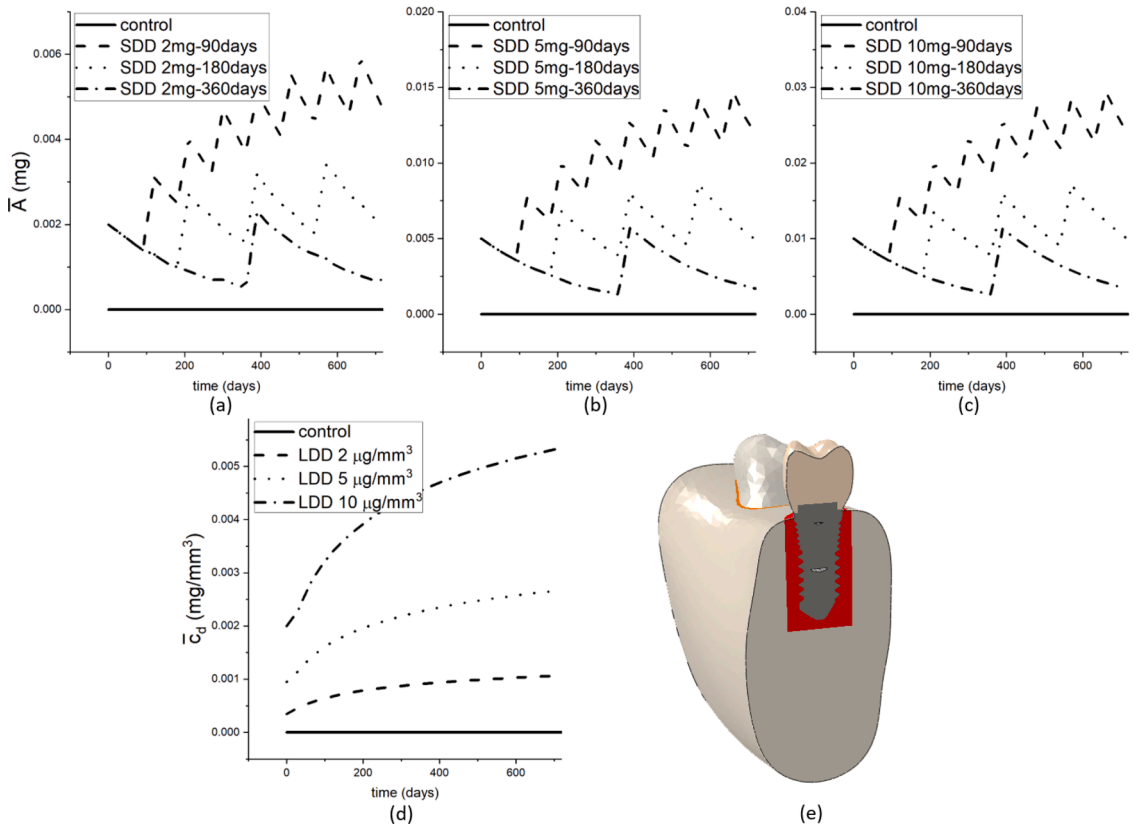

Fig. 6. Evolution of the averaged amount of drug in the layer around the implant after systemic drug delivery (SDD): (a) 2 mg every 90, 180, and 360 days, (b) 5 mg every 90, 180, and 360 days, (c) 10 mg every 90, 180, and 360 days; and (d) in local drug delivery (LDD) with 2, 5, and 10 $\mu g/mm^3$ of Zoledronate, and (e) cross-sectional view of the geometry with 1 mm bone layer around the implant (red section in the figure) for volume averaging. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

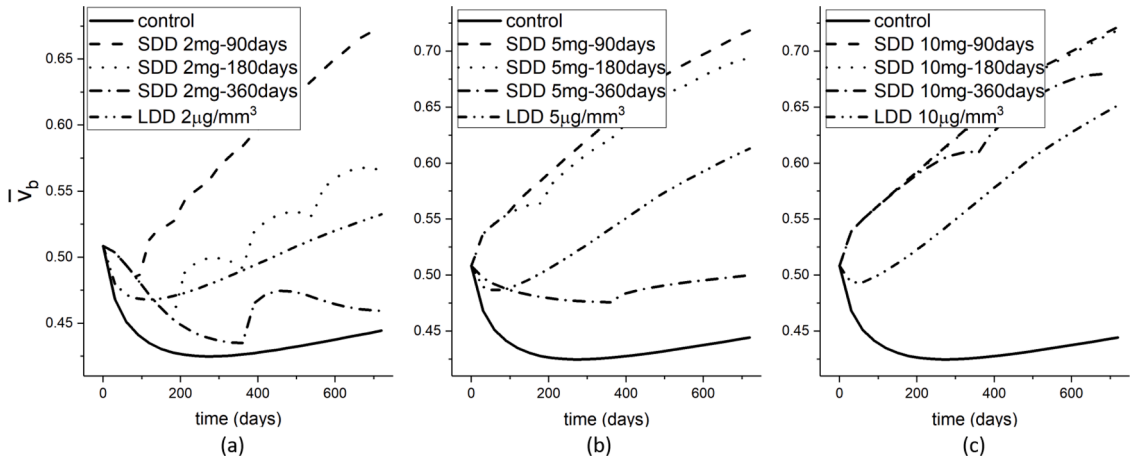

Fig. 7. Evolution of the averaged bone volume fraction in a 1 mm layer around the implant with different doses of coated and systemic Zoledronate: (a) 2 $\mu g\ /mm^3$ with LDD, 2 mg with SDD every 90, 180, and 360 days, (b) 5 $\mu g/mm^3$ with LDD, 5 mg with SDD every 90, 180, and 360 days, and (c) 10 $\mu g\ /mm^3$ with LDD, 10 mg with SDD every 90, 180, and 360 days.

volume fraction, damage, ash fraction, and bone mineral density are shown in Figs. 6–10. These magnitudes were obtained by averaging the distributions of such magnitudes within a 1 mm bone layer around the implant as shown in Fig. 6e.

$$\overline{(\bullet)} = \frac{\int (\bullet) dV}{\int dV} \tag{9}$$

where $(\bar{\bullet})$ indicates the averaged quantity in volume V.

Fig. 6 a–c show the temporal variation of the drug amount in the SDD case with doses of 2, 5, and 10 mg of Zoledronate for 90, 180, and 360 days. Fig. 6d shows the evolution of the drug concentration in the LDD case after application of doses of 2, 5, and 10 $\mu g/mm^3$ of coated Zoledronate. As the amount of coated drug increases, the amount of drug

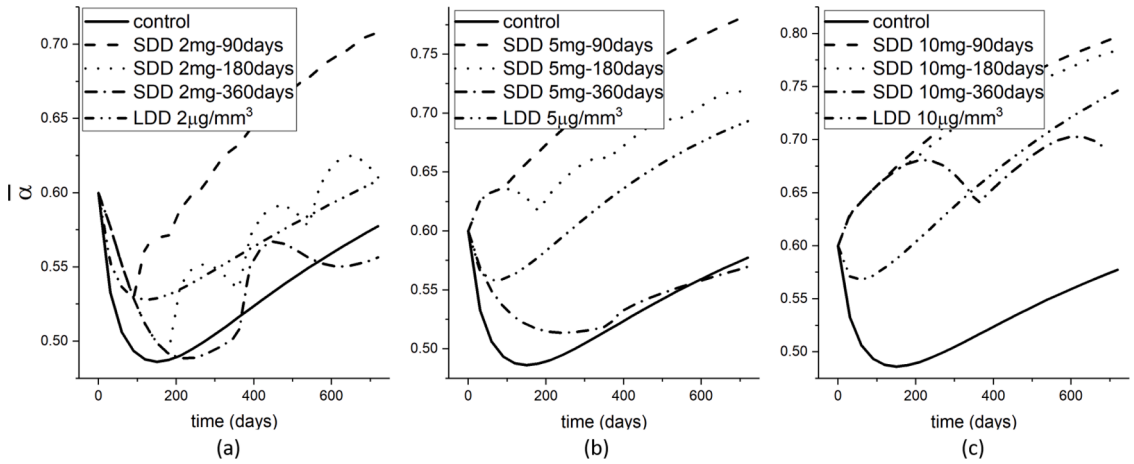

Fig. 8. Evolution of the averaged ash fraction in a 1 mm layer around the implant with different doses of coated and systemic Zoledronate: (a) 2 μg /mm^3 with LDD, 2 mg with SDD every 90, 180, and 360 days, (b) 5 $\mu g/mm^3$ with LDD, 5 mg with SDD every 90, 180, and 360 days, and (c) 10 $\mu g/mm^3$ with LDD, 10 mg with SDD every 90, 180, and 360 days.

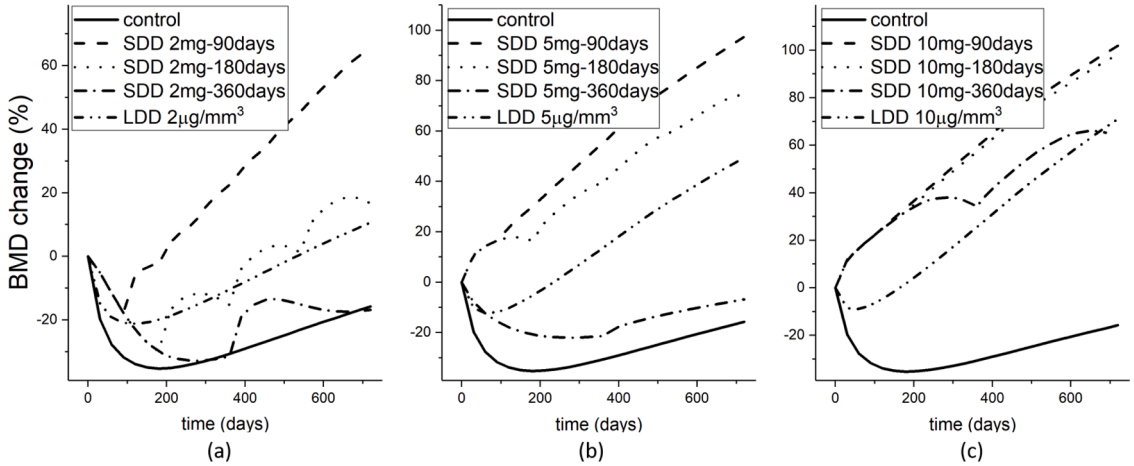

Fig. 9. Evolution of averaged bone mineral density change in a 1 mm layer around the implant with different doses of coated and systemic Zoledronate: (a) 2 μg /mm^3 with LDD, 2 mg with SDD every 90, 180, and 360 days, (b) 5 $\mu g/mm^3$ with LDD, 5 mg with SDD every 90, 180, and 360 days, and (c) 10 μg /mm^3 with LDD, 10 mg with SDD every 90, 180, and 360 days.

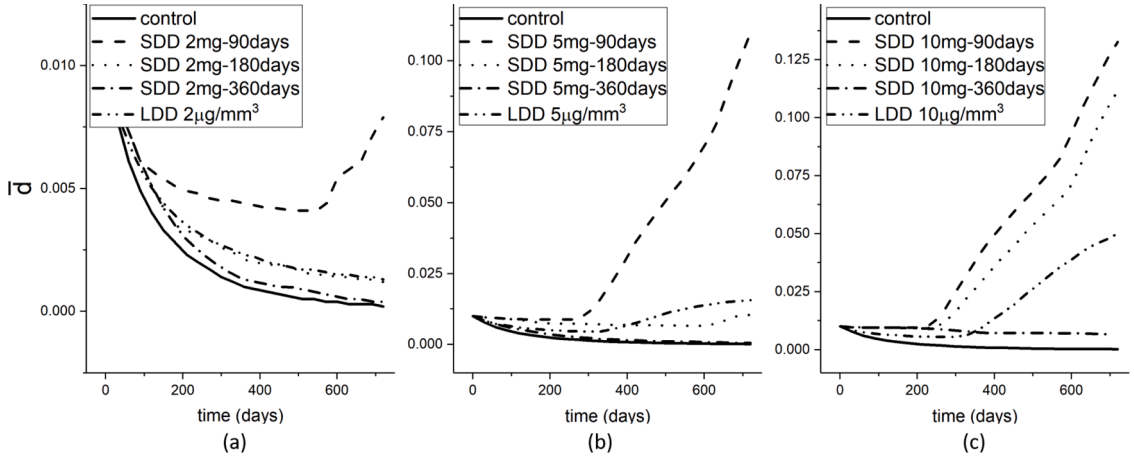

Fig. 10. Evolution of averaged damage in a 1 mm layer around the implant with different doses of coated and systemic Zoledronate: (a) 2 μg /mm^3 with LDD, 2 mg with SDD every 90, 180, and 360 days, (b) 5 $\mu g/mm^3$ with LDD, 5 mg with SDD every 90, 180, and 360 days, and (c) 10 $\mu g/mm^3$ with LDD, 10 mg with SDD every 90, 180, and 360 days.

that penetrates bone also increases, while decreasing the dosage period also increases the drug amount in each interval. These higher drug concentrations affect osteoclast activity, as clearly expressed by Eq. (4).

Fig. 7 shows the averaged bone volume fraction evolution in the control case and in the LDD and SDD situations over the layer depicted in Fig. 6e. In each case, the SDD-90 days shows the highest increase in bone volume fraction. The bone volume fraction in the LDD case with 2 and 5 $\mu g/mm^3$ doses is greater than in the SDD case for an interval of 360 days. In Fig. 7a the curve associated with LDD 2 $\mu g/mm^3$ is close to SDD 2mg-180 days compared to the other curves, while a more significant bone volume fraction can be observed with dose of a 10 mg of SDD in all time intervals, in comparison to LDD.

The average volumetric changes of mineralization are shown in Fig. 8. From this figure, it is clear that the mineralization in the 90-day interval is higher for any amount of drug in the SDD case than for other intervals and the LDD and the control cases. In the SDD situation and after 360-day interval, mineralization is lower than for all LDD doses and even lower than that in the control sample. The mineralization (Fig. 8a) is almost the same for the LDD-2 $\mu g/mm^3$ and SDD-2mg cases at the end of the simulation. Also, for the SDD-10mg dose, mineralization is almost identical at 90 and 180 days intervals.

The bone mineral content (BMC (g)) is an important bone measure that can be determined by absorptiometry and depends on the total volume (TV), bone apparent density (ρ) and bone ash fraction (α) as BMC $=$ TV$\times$ $\rho\times$ α. On the other hand, bone mineral density (BMD) refers to the amount of bone mineral in bone tissue. Assuming that the bone and total volume remain proportional along time, the BMD's percentage changes with respect to the initial value can be calculated by means of the following Eq. [35]:

$$\frac{\mathrm{BMD}}{\mathrm{BMD}_0}=\frac{v_b(1.41+1.29\alpha)\alpha}{v_{b0}(1.41+1.29\alpha_0)\alpha_0} \tag{10}$$

Fig. 9 d shows the volume percentage change in BMD relative to the initial value, calculated with Eq. (9) and (10). According to this figure, the amount of BMD in a layer around the implant increases when increasing the initial dose of coated Bisphosphonate. By comparing the LDD-2 $\mu g/mm^3$ with the SDD-2 mg doses for different periods of 90, 180, and 360 days, the percentage changes from the control case are 26, 80, 32, and -1 %. Therefore, the BMD becomes higher when applying the SDD for all dosages, except for 2 mg and 360 days when this increase is close to the control case.

Fig. 10 shows the effect of the drug on the averaged volume of damage in bone in the layer around the implant. As the amount of drug increases, damage also increases, and as the interval decreases, this increase intensifies. The amount of damage in Fig. 10a for both SDD and LDD applied in intervals of 180 days is approximately the same, while damage is lower for the SDD-360 days case than for LDD for all drug doses. The maximum amount of damage is observed for a dose of 10 mg-SDD with a 90-day interval, leading to an increase of about 165% compared to 10 $\mu g/mm^3$ LDD application.

4. Discussion

According to the different studies related to drug delivery of Bisphosphonates in orthopedics, the use of this therapy is one of the best methods to overcome the problem of osteoporosis. In this regard, some studies [9,36,37] have confirmed the positive impact of systemic Bisphosphonate treatment around the implant. The most crucial drawback of Bisphosphonates is their low bioavailability [38]. Side effects such as fever, stomach ulcers, headache, and bone pain have also been observed after systemic treatment of Bisphosphonates [39–41]. To avoid these side effects and to increase bioavailability, local treatment can be used as Bisphosphonates are suitable candidates for local therapy due to their high adhesion to bone [28].

One of the main objectives of this study was to investigate the effect of LDD on the success of dental implants in osteoporotic patients by comparing it with SDD. For this purpose, the success of dental implants in patients with osteoporosis was evaluated by examining the bone remodeling evolution in the vicinity of implants either receiving systemic drug delivery or coated with different doses of Bisphosphonate. A mechanical-chemical-biological bone remodeling model presented in a previous study [19] was used to assess the effect of the different doses of Bisphosphonate. Using Fick's diffusion and combining it with the bone remodeling model, the impact of local Zoledronate treatment on the dental implant was simulated. Also, the impact of drug consumption on mineralization and, finally, on the mechanical properties of bone were studied.

Few studies have been performed to compare the systemic and local effects of drugs around implants. These studies show an increase in implant fixation and osseointegration due to systemic and local use of Bisphosphonates [42,43]. As Abtahi et al. [44] showed that systemic use of the drug increases the risk of increased osteonecrosis in the jaw, and bone loss. Meraw and Reeve [11], Meraw et al. [12] investigated the local effect of sodium alendronate on bone formation around dental implants in adult dogs. Their results showed a significant impact of topical alendronate in increasing bone formation around dental implants. Lugero et al. [45] examined the osseointegration process around Titanium implants in two cases of healthy and osteoporotic tibial bone in female rabbits. The use of the drug affects bone remodeling and related properties such as mineralization and damage and evolution of the bone volume fraction and density.

Mechanical and biological factors involved in the healing process are significantly affected by aging and osteoporosis [46]. Therefore, bone properties after implantation contribute to the implant success. Drug-delivering systems change these properties promoting implant stability in the initial stages of implantation. The results of this study confirm other clinical and animal studies on the use of drugs to increase the fixation efficacy of implants [9,16,47–49]. Our results showed that topical drug delivery around the dental implant improves the bone volume fraction locally. As shown in Fig. 3, this is more evident when increasing the drug dose. It is also observed that reducing the period of drug administration in SDD increases the drug's effect and ultimately increases the volume fraction, mineralization and damage. Increasing the ash fraction increases bone brittleness and damage. These results indicate that increasing mineralization increases bone brittleness and damage (see Figs. 4 and 5), since microcracks propagate easier in regions with higher mineralization [50]. The increase in damage over a period of 90 days and a dose of 10 mg is significant (Fig. 10c).

By comparing the results of LDD with SDD, it can be concluded that LDD, unlike SDD that affects the entire bone, only affects the region around the implant. For example, Figs. 3-4 clearly show that the bone volume fraction and the ash fraction increase only in the bone around the implant. On the contrary, in SDD, these magnitudes increased uniformly throughout the whole bone. This implies that BMD, increases while for LDD treatment, the averaged BMD around the implant, first shows a decreasing trend and then an increasing one. This indicates that the bone far from the implant is not affected by the drug and, consequently, bone remodeling occurs naturally in such far regions.

Studies as [51–53] showed that mineralization and micro-damage also increase with drug treatment. Similarly, our results show that increasing the drug dose promotes higher mineralization, bone volume fraction, and damage in all types of bone. For denser bone that does not require drug treatment, drug provision, even with low doses, causes bone to become brittle, and the damage level increases up to its maximum level. The ash fraction also increases with the drug dose. In the drug-free state, the mineralized part of the bone decreases due to the action of the osteoclasts and the bone resorption that accompanies the filling and mineralization of bone by the osteoblasts. The drug inhibits osteoclast activity and thus reduces resorption, resulting in increased bone volume fraction, bone mineralization and ash fraction. On the other hand, due to the effect of Calcium on fatigue life, bones become

brittle, and damage increases. Also, since Bisphosphonates adhere to the bone surface, the mineralized surface of the bone is less exposed to resorption by osteoclasts, so mineralization increases, which reduces the bone fatigue lifespan (see Eq. (5)–(8)).

Our results also show that the bone volume fraction in the bottom part of the apex of implant and roots of implants reduces in the control case (Fig. 3b-c), but using a drug coating on the implant increases the bone volume fraction in such regions (Fig. 3j–o). The increase in bone volume fraction around the dental implant can be seen in Fig. 5. This higher bone volume fraction is got without side effects in locations far from the implant, such as higher mineralization, which confirms the previous study conducted on systemic Ibandronate delivery [19]. All these results demonstrate the improvement in implant fixation induced by implant coating that may overcome the limitations of a poor bone quality. LDD of Bisphosphonate also adheres to the bone around the implant for a longer periods [9]. As a clinical conclusion, osteoporosis may affect the healing period after implantation, but dental implant ossification may occur even in osteoporotic bone [54], especially if helped by Bisphosphonates.

Like any other study, the one presented here has limitations that should be considered in the future. Due to the lack of information about race, age, sex, etc., the biological parameters used in this study are generic and based on previous studies. In the future, it would be better to fix the model parameters to the specific patient's bone tissue characteristics, thus driving to more accurate results within the new framework of Precision Personalized Medicine. The diffusion coefficient used for Zoledronate is based on previous studies for spongy bone. In this study, we used a constant diffusion coefficient for all bone types. Using a diffusion coefficient for different types of bone can improve the results. Also, obtaining the diffusion coefficient of different drugs can make it possible to compare other medicines. Finally, to obtain the effect of systemic drug delivery on bone remodeling, a 1-chamber model for the drug was used, while increasing the number of studied chambers can be effective in obtaining more accurate results. Recently, a study [55] has shown the impact of Bisphosphonates on bone formation activity by disrupting the onset of osteoblast activity. Osteoporotic conditions are accompanied by a dysregulation of the signaling pathway and therefore on cell differentiation. This includes disruption in OPG production due to estrogen deficiency, decrease in TGF_{β} production, and reduction in osteoblasts progenitor differentiation due to glucocorticoid-induced osteoporosis [56,57]. These aspects have not been considered in this approach, which is a limitation to overcome in subsequent studies.

5. Conclusion

Success in dental implants may be impaired when a disease such as osteoporosis appears. Antiresorptive drugs can be used in patients with osteoporosis or, in general, with low bone density since this condition increases the risk of implant failure. Our work concludes that local drug delivery only affects bone around the implant, and the local treatment reduces the side effects of systemic drug delivery, such as brittleness and damage. It is the effect of the drug on the activity of osteoclasts, which reduces the resorption of microcracks that osteoclasts would have removed remain unchanged, so the accumulation of damage and a higher mineralization increases bone brittleness.

It can be concluded that despite the many limitations in bone remodeling models, as well as insufficient knowledge and accuracy of many of the parameters involved, the model presented herein is a step forward in better understanding and quantifying this essential biological process. Also, the results obtained reflect many of the results in independent clinical studies on the systemic and local effect of Bisphosphonates around implants.

Ethical approval

Not required.

Funding

None.

Declaration of Competing Interest

None declared.

All authors must disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

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