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Preliminary results of the bisphosphonate-related osteonecrosis effect on rat jaws undergoing three-point bending using finite element analyzes

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1. Introduction

Bisphosphonates-related osteonecrosis of jaws (BRONJ) is a major side effect of bisphosphonate (BP) medications, occurring after tooth extraction (Ledouble et al. 2022). The effects of such adjunctive therapeutics on jaw mechanical response are poorly investigated in preclinical studies due to the lack of reproducible animal model but also because of the difficulty to set appropriate experiments. For instance, Ledouble et al. 2022 pointed out the effect on rat hemimandible stiffness and force peak during three-

point bending tests. Such a mechanical test has already been conducted by Lezón et al., 2017 pointing out same order of magnitudes. However, the direct comparison could not be made due to the lack of intrinsic parameters. The purpose of this study is to identify such mechanical parameters by using 3D geometrical reconstruction in combination with finite element analyzes through an inverse approach (Laurent et al., 2022).

2. Methods

2.1 Samples

Thanks to the approval of the Committee on Animal Care of Reims University (n°2020062216423895v3), male Wistar rats were treated with zoledronate (ZA) a BP combined with dexamethasone (DEX) an approved treatment for BRONJ preclinical models (Aguirre et al., 2021). Each mandible was separated in two hemimandibles by cutting the incisive connecting ligament before mechanical testing (Ledouble et al., 2022).

2.2 Tomography and geometry reconstruction

Prior to mechanical testing, left hemimandible samples were scanned through x-ray computed tomography (CT, EasyTom nano, RX Solutions) with a resolution of 20 microns. The sample geometries were then reconstructed using 3Dslicer and various Python libraries.

2.3 Finite element analysis

The three-point bending tests were reproduced with the help of a finite element model using Abaqus/CAE 2022[®] software. Frictionless contacts were considered in between the bony structure and the three-point bending pins. The bone tissue was assumed to be isotropic linear elastic with a uniformly distributed properties. The initial value of Young's modulus was set to 3GPa and a Poisson ratio was taken equal to 0.3 (Laurent et al. 2022).

2.4 Optimization

To reproduce the experimental response, simulated force-displacement curve was confronted to experimental ones of both symmetrical hemimandibles. Due to the linear behavior of the chosen material, the optimization was made by comparison of maximal forces to get a correction coefficient leading to an optimal fitting.

3. Results and discussion

Height mandibles were tested: four control (CTRL) and four with ZA/DEX treatment which represent 16 hemimandibles. The segmentation and 3D reconstruction of the hemimandible allowed the computation of center of inertia which appeared to be

below second and third molars. This location was chosen to apply the mechanical load as it was done in the work of Lezón et al., 2017 to keep the sample stable on the support pins. Representative control samples were chosen to present the quality of the procedure, as shown in Figure 1.

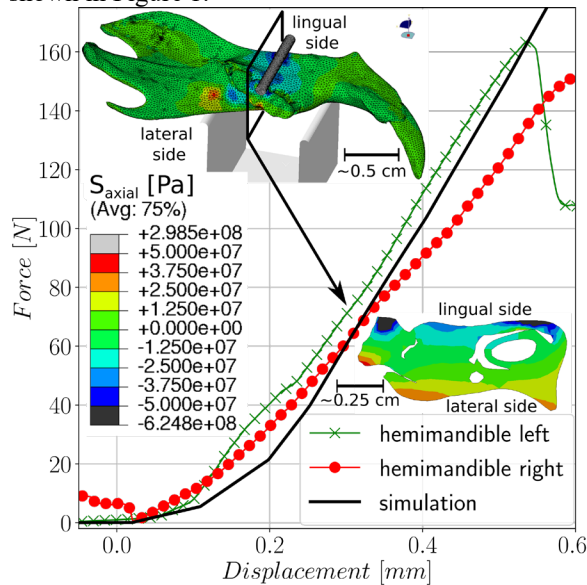


Figure 1. Force displacement response of a pair of representative hemimandibles (left and right) with superimposed the finite element simulation result for 0.55mm imposed displacement. Insets show the axial stress distribution in the whole structure and in the cross section below the loading pin. credit: A Baldit

First of all, the experimental results showed the symmetry of the mechanical test in between two hemimandibles of a same mandible.

	Control	ZA/DEX
Porosity [%]	14.79±2.11	13.00±1.82
Young modulus [GPa]	3.40±0.62*	4.50±0.14*

Table 1. Statistical results with $n=4$ which represents 8 samples by symmetry (* $p=0.01$ through t -test statistics). credit: A Baldit

As expected the axial stress field points out stress concentration near loading and support pins. The cross section below the loading pin shows that the lingual side is subjected to compressive stress, while the lateral side undergoes tension. On the other hand, it highlights a limitation about the choice of the uniformly distributed Young’s modulus since the bone and the teeth are fused and considered as a unique part with same mechanical properties. Such idealization may not be realistic. Although, the experimental tests of Ledouble et al., 2022 pointed out that removing teeth did not significantly affect the mechanical response of the structure as the measured stiffness were in the range of the CTRL samples.

Thanks to the 3D reconstruction, the global porosity of hemimandibles summarized in Table 1 appears to be affected by the ZA/DEX treatment that blocks bone remodeling leading to a decrease in bone porosity. Eventually, the preliminary results point out the effect of the treatment with an increase of the bone effective Young’s modulus. This stiffening of the structure is perfectly in tune with the side effects of ZA/DEX treatments.

4. Conclusions

The presented procedure enables to obtain an estimate of the intrinsic mechanical properties of a rat BRONJ model. The associated results give a consistent explanation of Ledouble et al., 2022 observations that could not be covered by the previously estimated stiffness. The 3D mesh generation as well as the porosity estimates raise questions about assumption functions from tomography accuracy to surface smoothing. They can affect the considered hemimandible structures and so on the computational cost as well as the mechanical properties. Microstructure tests, such as nanoindentation, would provide insight about local mechanical properties. Finally, the tomography gives also access to densities that could be used for heterogeneous Young’s modulus estimation as presented in Laurent et al., 2022.

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Conflict of Interest Statement

None

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