BACHELOR'S THESIS / BIOMEDICAL ENGINEERING 2022

Osteoporosis pharmacological treatment evaluation through femoral biomechanical response using DXA-based 3D Finite Element Modelling

Marina M. Pérez Tomàs

Universitat Pompeu Fabra
Barcelona

Osteoporosis pharmacological treatment evaluation through femoral biomechanical response using DXA-based 3D Finite Element Modelling

Marina M. Pérez Tomàs

Bachelor's Thesis UPF 2021/2022

Thesis Supervisor(s): Dr. Carlos Ruiz Wills

BCN MedTech research group
(Biomechanics and Mechanobiology Team)

In loving memory of my departed grandmother, La Chepita. I dedicate this work to you. I know you would be proud of everything I have accomplished. Thanks for guarding me and being by my side in every step I take. I love and miss you so very much.

upf. Universitat Pompeu Fabra Barcelona

Acknowledgments

I would like to give a special thanks to my beloved teacher, tutor, and friend Carlos Ruiz Wills who helped me throughout the entire process of my bachelor's thesis with so much patience and dedication. He always gave me the confidence to make decisions and lead me to do extraordinary things that I didn't even know I was capable of. This work would not have been possible without his guidance and support. So many times, he repeated to me that I must trust myself; No worries, I'm slowly but surely getting there.

What can I say about the amazing friends I have made over the years in the degree. The ones who have helped me and have been there for me whenever I needed them. You have made me feel at home.

I would also like to express my gratitude to my family. The ones who made me be where I am. That despite the hard times, we will always have each other. Those who have always been supportive during my life, encouraging me to achieve my goals and challenge myself to do my best. The ones who have taught me that the sky is the limit.

I can't thank them enough.

All this is for you!
Thank you very much
from the bottom of my heart.

Summary/Abstract

Osteoporotic hip fractures are one of the most severe an individual can suffer due to their high mortality rate. There are pharmacological treatments such as Alendronate (AL), Denosumab (DMAB), and Teriparatide (PTH) that help on reducing these fractures. Depending on their mechanism of action, they improve the bone mineral density (BMD) of either the cortical or the trabecular bone. Dual-Energy X-ray absorptiometry (DXA) is used to measure this parameter and quantifies bone improvement with these therapies. Several studies had combined Finite Element (FE) models with medical images to estimate fracture prediction. Yet, there is no evidence of using such methodology to study drug effectiveness by assessing the biomechanical response of the bone. Thus, the aim of this study is to evaluate different osteoporotic treatments using DXA 3D FE modeling and analyze the Major Principal Stress (MPS) and Major Principal Strain (MPE). A cohort of 155 osteoporotic patients were divided into four groups AL (n=54), DMAB (n=33), PTH (n=31), and a control group designated as NAIVE (n=37). Two DXA acquisitions were provided before and after 1-2 years of taking the medication. A side-fall simulation was evaluated with a patient-specific force applied in the femoral head where the distal bone was fixed, and the trochanter was constrained in the direction of the force. The biomechanical parameters: volumetric BMD (vBMD), MPS, and MPE were analyzed by tissue (cortical or trabecular), zone (neck or trochanter), and by its combination. Results showed decreasing strain when vBMD increases, indicating that the bone deforms less due to the reinforcement of its structure. DMAB had the highest outcomes, while the trabecular bone and the trochanter area were the most reinforced. Overall, this study suggests that DXA 3D finite element models might be a valuable tool in clinical practice for evaluating pharmacological treatment for osteoporosis.

Keywords

Osteoporosis, hip fracture, drug efficacy, DXA, Finite Element Model

Prologue

Currently, it has been estimated that more than 200 million people are suffering from osteoporosis. According to recent statistics from the International Osteoporosis Foundation, worldwide, half of all women will break bones due to osteoporosis. Fractures are the most critical clinical complication of osteoporosis. It has been reported that 86% of hip fractures occur in individuals aged 65 years and older that normally died within the first year. And the few people able to survive usually end up suffering from depression as a result of not being capable to do daily activities on their own, such as getting up or walking.

Therefore, prescribing the right pharmacological treatment is crucial for reducing the statistics and deaths associated with hip fractures. The current method in which these therapies are being prescribed is in no way endorsed. It is totally indicated by the criteria of the physicians based on their experience. To analyze the efficacy of the indicated medication is by looking at 3D medical images from both before starting the treatment and after many years of taking the medication. Leading to a tremendous delayed conclusion on whether it was the appropriate drug for the patient.

There had been various studies aiming to support this clinical problem by using computational tools as Finite Element (FE) models that were traditionally intended to predict fracture probability. These models when combined with a 3D medical imaging, such as osteoporosis diagnosis techniques, provide patient-specific information and properties that can deliver an important assessment to fracture risk. The only drawback of FE models combined with QCT is the fact they are very expensive with high radiation carrying.

DXA is more accessible and with less radiation emission comparing to QCT. The fusion of DXA acquisitions with three-dimensional FE models is powerful in analyzing and assisting this decision-making. This methodology is able to help clinicians identify which pharmacological treatment would be best for each patient, improving fragility fracture rates and therefore complications and deaths. This unique combination is an innovative tool for personalized medicine. Helping medical institutions which are gradually progressing by adopting decision support mechanisms to improve care for patient outcomes and reduce errors.

upf. Universitat Pompeu Fabra Barcelona

Index

List of Figures

List of Tables

1 Introduction

1.1 The Problem and the Motivation

Hip fractures disturb millions of lives worldwide. This issue has a high social, economic, and health impact that usually affects elderly and post-menopausal women. Above 20% die within the first year, and most of the survivors are not capable of doing daily activities [1]. Statistics show that approximately 1 in 3 women and 1 in 5 men over 50 years old will suffer from a fragility fracture [2]. These numbers are continuously increasing with the progressive aging of the population. As a result, over 248.487 deaths were directly related to hip fractures in the European Union (EU) in 2019 [3].

Osteoporosis is the main cause of these fractures. According to the World Health Organization (WHO), it was estimated that 27.6 million people in the EU suffer from this pathology [2]. This disease is characterized by the weakening of bones, increasing their fragility and fracture risk.

The gold standard method to detect osteoporosis is through the evaluation of the bone mineral density (BMD) using Dual-energy X-ray Absorptiometry (DXA). However, the capability of DXA for fracture prediction is poor [4]. Quantitative Computer Tomography (QCT) can provide a volumetric distribution of the BMD. QCT is capable of differentiating cortical and trabecular bone but exposes the patient to high radiation and it is expensive [4].

Osteoporosis can be tackled by pharmacological treatments. Bisphosphonates are the most used, nonetheless, physicians prescribe the treatment based on their own experience and criteria. Treatment effectiveness is usually achieved by osteoporosis diagnosis techniques. Indeed, the changes in BMD before and after the treatment can provide treatment efficacy. Yet, the time between images acquisition might take years [3].

Lately, computational tools, like finite elements (FE) modelling [5], can provide valuable information regarding bone mechanical response. In fact, most of the FE models available aim to predict the fracture. The combination of QCT imaging and 3D FE models allowed the estimation of bone strength which led to a classification power up to 90%. Such models have been used for the evaluation of osteoporosis treatments too [6]. Nevertheless, the regular use of such a model is limited due to the high cost and radiation dose.

Advanced DXA image techniques have shown the capacity to assess the volumetric distribution of BMD for both cortical and trabecular bone. This methodology has been used to study the efficacy of different pharmacological treatments for osteoporosis [7]. Recently, DXA-based 3D FE models addressed, with high accuracy, the discrimination of fracture and non-fracture cases. However, to the date, the efficacy of such models in the evaluation of osteoporosis treatments remains unexplored.

1.2 The Objective

The aim of this study is to evaluate the effectiveness of different pharmacological treatments using the biomechanical parameters: Mayor Principal Stress (MPS) and Strain (MPE) obtained from patient-specific DXA-based 3D finite element simulations. The idea is to create a tool that allows generating a complete study of the efficiency of the drug and assists the clinical decision-making for a personalized solution for each patient.

2 State of the Art

2.1 The Bone

Bone is an organ made up of hard tissues that form the endoskeleton of many animals such as humans. The structure and composition of the tissue provide many purposes, being locomotion and protection of vital organs, the two main ones [8]. Bones are organized into two tissues: The cortical section, which is considered the compact tissue that forms the surface layers of all bones, and the trabecular bone, a sponge-like tissue that is highly porous, situated at the terminations of long bones and inner parts of flat bones (Figure 1) [9][10].

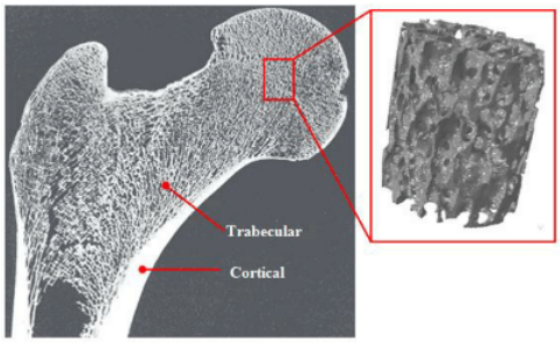

Figure 1: Tissue differentiation on a coronal slice from the proximal femur [11]

2.1.1 Mechanical Properties

The bone is a heterogeneous composite material that has a unique combination of strength and elasticity. Consequently, the biomechanical behavior of the tissue is complicated to understand and analyze due to its heterogeneity and anisotropy [12]. The anisotropic behavior of the bone is reflected in different mechanical responses depending on the direction of the force applied.

2.1.2 Bone Remodeling

Bone is produced by cells called osteocytes, which have osteoblasts and osteoclasts. Osteoblasts are cells that produce bone in reaction to mechanical stresses and additional growth factors such as hormones. On the other hand, osteoclasts are cells that break down and reabsorb bone (Figure 2). Typically, the body generates new bone faster than the absorption of old bone. Such process is called bone remodeling.

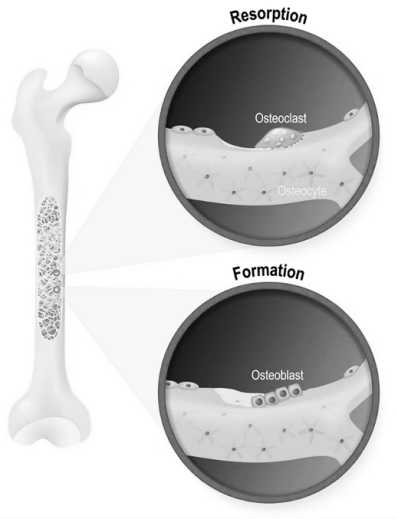

Figure 2: Osteoblast and Osteoclast in bone remodeling [13]

2.2 Osteoporosis

Osteoporotic patients present a disruption in this cell activity leading to more porous bones, with more significant number and size of cavities inside them (Figure 3). Making the tissue less shock resistance. It also generates a disbalance in the body's hormones, as in Thyroid-stimulating hormone (TSH) which normally on high levels has a protective role on bone mass.

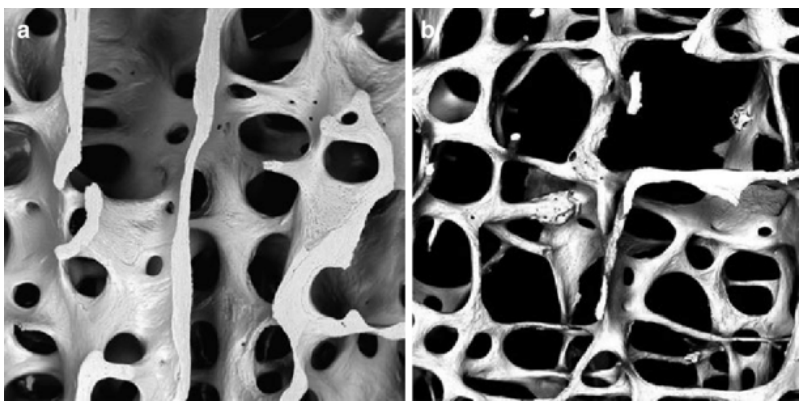

Figure 3: (left) Healthy femur with a standard bone matrix. (right) Osteoporotic femur with reduced BMD. [14]

Factors like the reduced levels of estrogen, testosterone, Insulin-like growth factor 1 (IGF1), and vitamin D; and the increase of cortisol, parathyroid hormone, and follicle-stimulating hormone (FSH) can generate bone mass loss. Hence, the propensity of menopausal women to suffer a higher incidence of osteoporosis is related to this disbalance in hormones levels. Specifically, the decrease in estrogen (commonly referred to as estradiol). Table 1 shows the exact action on bone cells of each hormone [7].

Hormones	Molecular Action	Role
TSH	↑ osteoblast differentiation ↓ osteoclast formation and survival	+
Cortisol	↓ maturation, lifespan and function of osteoblast	-
Estradiol	↑ osteoblast proliferation and differentiation ↓ osteoclast differentiation	+
Testosterone	↑ osteoblast proliferation and differentiation	+
FSH	↑ osteoblast proliferation	-
Parathyroid Hormone	↑ osteoclast proliferation ↑ osteoblast proliferation	-
Vitamin D	↑ osteoblast differentiation	+
IGF1	↑ osteoblast proliferation and differentiation ↑ osteoblast proliferation	+

Table 1: The role of hormones on bone mass [7]

Density loss affects bone mechanical response. Indeed, low-density values are associated with weakening; reducing its capability to resist loads. Bone behaves similarly to a ceramic material due to its biomechanical properties. Thus, the fragile tissue can break easily with a slight overload or load that a healthy bone could normally withstand.

2.2.1 Osteoporotic Hip Fracture

Osteoporosis is also known as a silent illness due to its lack of symptoms because patients cannot feel their bones weakening. Primary signs besides bone breakages include noticing the shortening of the patient's height [15]. Osteoporotic patients mostly break their bones by simply falling or doing daily activities due to their low BMD. These often happen in the elderly due to their reduced vision, mobility, or balance problems, and depending on the fracture severity patients might require surgery.

Hip fractures are caused by an injury focused on the upper portion of the femur where the complications and recuperation can vary depending on the area where the breakage had occurred. The most common areas a hip is prone to break are the femoral neck and trochanter represented in Figure 3. As the femoral neck is the narrowest part of the femur, the structure is normally not able to support a direct force applied. Femoral neck fractures are particularly problematic, as it often interrupts the blood supply to the head of the femur, causing severe pain and leading to arthritis development. On the other hand, trochanter hip fractures usually result from a fall or direct hit impact [16].

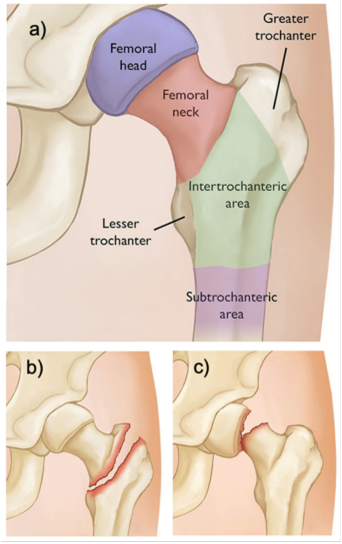

Figure 4: (a) Femur zone areas. b) Intertrochanter femur fracture. c) Neck femur fracture. [17]

2.2.2 Treatments

Due to its complex awareness of osteoporosis symptoms, it is estimated that 20% of patients that suffered an osteoporotic fracture were not treated or even diagnosed with osteoporosis [15].

Osteoporosis treatments aim to enhance BMD. The therapies have two different action mechanism approaches: 1) inhibit the osteoclasts' actions and produce less bone degradation, and 2) induce the activity of the osteoblasts, generating a more amount of bone mass.

There are treatments based on bisphosphonates, calcitonin, hormones, and estrogen. Bisphosphonates are the gold standard to treat osteoporosis, reducing bone fractures by decreasing bone reabsorption. In brief, bisphosphonates reduce osteoclast activity, cutting down the excessive bone resorption [18].

The most common bisphosphonate is Alendronate (AL), which acts with the primary action mechanism of being recognized by osteoclast and converts into an

Adenosine triphosphate (ATP) toxic analog to suppress and reduce osteoclast activity. It is the most studied bisphosphonate in post-menopause osteoporosis. Theoretically, AL improves better the cortical bone. Literature [19] showed that AL increases the BMD in the column and the hip and decreases the fragility fractures by 55% . It is administrated with a daily dose of 10 mg or taken in a weekly dose of 70 mg [20].

Likewise, Denosumab (DMAB) is a human monoclonal antibody (IgG2) whose mechanism of action inhibits osteoclast formation, function, and survival leading to minor bone reabsorption in both cortical and trabecular bone [21]. Even though, it is supposed to present higher density increases in the cortical bone. Previous works [22] presented DMAB risk reduction of vertebral fracture in a 68% compared with a control group and increases BMD at the lumbar spine, total hip more than alendronate and control group. It can be found as a daily subcutaneous injection.

And finally, Teriparatide (PTH) contains a synthetic analog of the human parathyroid hormone and consists of its active portion. Its action mechanism includes stimulating bone formation by directly activating the osteoblasts. In theory, PTH is expected to improve the trabecular bone on a larger scale. Literature [23] indicates that PTH reduced the risk of new vertebral fractures by 65% and the risk of new moderate or severe vertebral fractures by 90%. It can also be administrated as a daily injection [24]. Even though, there is an extensive list of osteoporotic pharmacological treatments.

2.2.3 Evaluation of the treatment

Pharmacological treatment evaluation can be measured using different approaches. The most common is through the quantification of BMD before and after taking the medical treatment with 3D medical images such as its diagnoses techniques. Another approach is the use of computational models, such as FE models.

R. Winzenrieth et al. [25] used a DXA-based 3D modeling approach to assess the effects of osteoporosis drugs (AL, DMAB, PTH, and a control group (NAÏVE)) with the strength changes on the cortical and trabecular bone at the femur. Results presented by the NAÏVE group showed non-significant decreases were observed in both trabecular and cortical BMD. While AL group significant increases were observed in both trabecular and cortical as well as DMAB. On the other hand, PTH exhibited a significant increase in the trabecular compartment but a non-significant increase in the cortical leading to a decrease in general BMD. This study showed the great capacity of DXA models to measure pharmacological treatment evaluation. But, the FEM approach can provide more specific information in tissue and critical zones. The method may include biomechanical parameters obtained by the response of the bone to a specific stimulus.

Tony M Keaveny et al. [26] used a 3D Finite Element Modelling obtained by

QCT to compare the effects of PTH and AL on vertebral strength changes and compared it to the measured BMD by both DXA and QCT. Results showed that both treatments had positive effects, they increased the vertebral compressive strength for at least 75% of the patients and exhibit larger increases in trabecular for PTH. Lastly, demonstrated that DXA failed to capture the treatment-induced biomechanical changes, particularly for alendronate. Changes in BMD from DXA were poorly correlated with the changes in FE strength. This is consistent with previous research [27] showing that DXA fails to adequately explain the efficacy of antiresorptive treatments.

Another study by Tony M Keaveny et al. [6] used a QCT-based 3D FE model to compare average strength changes at the hip for different osteoporotic treatments AL, PTH, and their combination (CMB) and then switched to either AL or placebo (PLB) in the second year. The 3D FEM–based biomechanical analyses provide a noninvasive clinical assessment of femoral strength where the 3 groups had an increase in overall femoral strength. But the large difference between PTH-PLB and PTH-AL reinforces the conclusion of following treatment of PTH with an antiresorptive agent, preserving the improvement achieved with PTH. Limitations showed that DXA is clearly restricted for analysis with 3D structures specifically in which changes are typically small. This study showed how powerful is the combination of these two techniques to analyzing osteoporotic pharmacological treatment effects on bones. Even though, understanding bone local behavior at the cortical and trabecular bone, and critical zones such as neck and trochanter would provide a complete insight into break-off fracture phenomena.

Lang Yang et al. [5] used a DXA-based FEM of the proximal femur to evaluate whether FE bone strength can predict hip fracture risk independently of BMD. To do so, an impact force was applied to a 2D FE model, exactly at the greater trochanter. The distal part of the femur was fixed, and the femoral head was restrained in the vertical direction. Results showed that estimated FE strength and BMD were positively correlated, but negatively correlated to fracture probabilities. Recently, DXA-based 3D FE models were used to address fracture classification [28]. With those models, a discrimination power of up to 90% for fracture and non-fracture cases was obtained. The major principal stress was proposed as a good classifier. Nevertheless, no DXA-based model, 2D or 3D, has been used for pharmacological treatment evaluation.

3 Methods

3.1 Patient Database

This study was carried out with a database from CETIR Grup Mèdic (Barcelona, Spain). A cohort of 155 subjects with osteoporosis, including both men and women (45 - 83 years old) was used. Equally, baseline and follow-up examinations were obtained with a DXA scan (GE Healthcare, Madison, WI, USA), following the rec-

ommendations of the instructions.

The subjects were divided into four different groups according to the received treatment: 54 for AL, 33 for DMAB, 31 for PTH, and a control group with no pharmacological treatment administrated (NAIVE) with 37 subjects.

3.2 Patient-Specific Model Generation

A software algorithm 3D-shaper was used to generate all 3D-geometry of each 2D DXA scan. In brief, the software generates a 3D mesh with a volumetric distribution of the BMD useing a Statistical Shape Model (SSM). The DXA scan is superposed with the morphologically most similar QCT image in their repertory and adapting it to generate the 3D model. Both cortical and trabecular bones were addressed.

All mesh models consisted of 26200 elements, cortical and trabecular bone were also included. Also, a volumetric density distribution was obtained for each subset. The detailed information of the mesh obtained can be seen in Table 2. The simulation was implemented in Abaqus 2018 (Dessault systèmes).

Area	Number of elements
Total	26200
Cortical	6900
Trabecular	19300
Neck	3762
Trochanter	13460

Table 2: Element number definition for reach tissue and zone.

3.2.1 Mechanical Properties

Bone was considered as an isotropic linear elastic material. The coefficient of Poisson (μ) was 0.3, and the Young modulus (E), was calculated in MPa from BMD distribution through the following empirical relationships [28].

$$\rho_{ash} = 0.87\,\rho_{QCT} + 0.079 \tag{1}$$

$$E_{trabecular} = 10200\,(\rho_{ash})^{2.01} \tag{2}$$

$$\rho_{app} = \frac{\rho_{ash}}{0.6} \tag{3}$$

$$E_{cortical} = 0.003715\,(\rho_{app})^{1.96} \tag{4}$$

where ρ_{ash} $[g/cm^3]$, is the ash density given by the QCT-like density obtained with 3D-Shaper, ρ_{app}, is the apparent density of the bone $[kg/m^3]$.

3.2.2 Boundary Conditions

Lateral fall simulations followed an experimental set up [29]. The diaphysis had 10^{o} from the ground, and 15^{o} of internal rotation. The distal part of the femur was fixed, and the great trochanter was constrained in the direction of the force (Figure 5). A patient-specific force, same for baseline and follow-up, was applied at the top of the femoral head following equation 5.

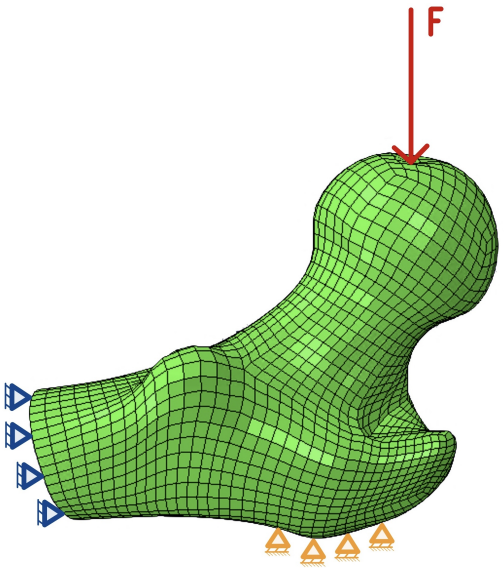

Figure 5: Lateral fall Boundary Conditions for the simulation

$$F = \sqrt{2\, g\, m_p\, h_c\, k_{st}} \tag{5}$$

$$h_c = 0.51\, h \tag{6}$$

Where g is the gravity, approached as 9.8 $[m/sg^2]$. The variables m_p is the mass of the patient [kg] and h_c is the height of the center of gravity related to the height of the patient [m], and lastly, k_{st} which represents the damping by the soft tissue covering the femur. It is related to the unidirectional stiffness and depends on whether the patient is man ($k_{st} = 90$ [N/mm]) or woman ($k_{st} = 71$ [N/mm]).

Changes between baseline and follow-up for integral, cortical, and trabecular bone were computed for volumetric BMD (vBMD) obtained from DXA and the major principal stress (MPS), and major principal strain (MPE) from the FE simulations. Such changes were evaluated by zone (neck and trochanter), tissue (cortical and trabecular), and both zone and tissue altogether.

The average value of all elements was computed in each model in the evaluated zones and tissues. A paired t-test with two-tailed distribution and p-value < 0.025 was implemented to evaluate the significance of the obtained data.

4 Results

4.1 Integral Bone Analysis

Follow-up vBMD mean values were higher than baseline for all treatments. On the other hand, MPS and MPE mean values decrease for AL, DMAB, and PTH, yet both parameters increased for the NAÏVE group (Table 3).

		vBMD [g/cm^3]	MPS [MPA]	MPE [mm/mm]
AL N=54	Baseline	0.342 ± 0.0402	21.225 ± 2.563	0.022 ± 0.00541
	Follow-up	0.348 ± 0.0423	20.967 ± 2.372	0.021 ± 0.00536
DMAB N=33	Baseline	0.274 ± 0.0320	21.787 ± 3.583	0.031 ± 0.00907
	Follow-up	0.281 ± 0.0389	21.077 ± 2.782	0.029 ± 0.00931
PTH N=31	Baseline	0.271 ± 0.0349	23.184 ± 3.315	0.034 ± 0.01017
	Follow-up	0.272 ± 0.0374	22.613 ± 3.143	0.033 ± 0.01109
NAIVE N=37	Baseline	0.315 ± 0.0373	21.579 ± 3.663	0.034 ± 0.01017
	Follow-up	0.313 ± 0.0372	21.891 ± 4.139	0.033 ± 0.01109

Table 3: Baseline and follow-up descriptive statistics for each treatment.

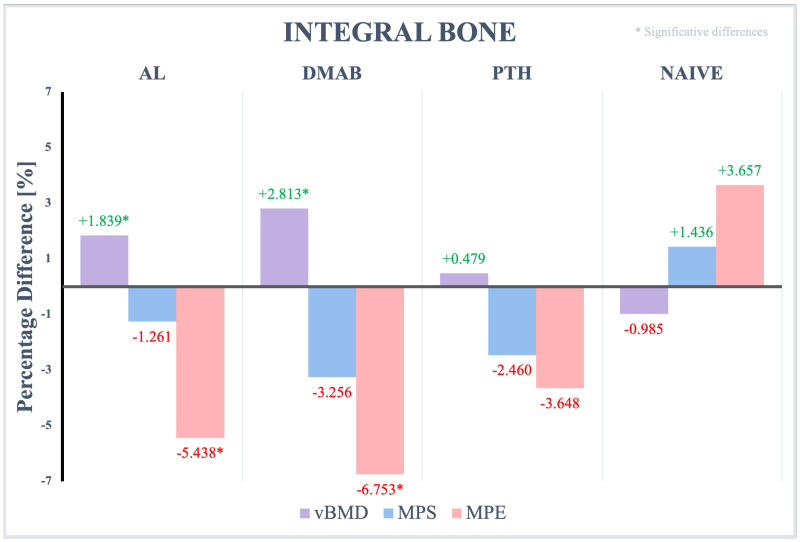

Figure 6: Integral bone percentage differences for vBMD, MPS, and MPE by treatment.

Figure 6. shows the percentage changes in vBMD, MPS, and MPE for all treatments and the NAÏVE group in the integral bone. The highest vBMD significant increase was obtained by DMAB with 2.81%, followed by AL with 1.84%. On the other hand, PTH showed a non-significant density increase of 0.48%. A significant decrease in the strain was obtained by DMAB and AL with 6.76% and 5.44%, respectively. Besides, PTH presents a 3.65% MPE decrease. On the contrary, decreased changes in vBMD while increases in MPE group were obtained in the NAÏVE group, with 0.99% and 3.66% correspondingly.

Regarding the MPS, decreased changes were obtained by all treatments. Such outcomes did not follow the expected biomechanical behavior of linear elastic materials. Consequently, the further analysis will focus only on the MPE parameter.

4.2 Tissue Analysis

Treatment	Tissue	vBMD	MPE
AL	Trabecular	+2.955*	-5.637*
	Cortical	+1.281	-3.780*
DMAB	Trabecular	+4.950*	-6.908*
	Cortical	+1.702	-5.557*
PTH	Trabecular	+3.387	-3.873
	Cortical	-1.037	-1.894
NAIVE	Trabecular	-1.534	+3.823
	Cortical	-0.647	+2.503

Table 4: Relative difference in percentage divided by tissue

Table 4. presents the change of vBMD and MPE by bone compartment. The trabecular bone was the compartment with higher differences in both vBMD and MPE. The most significant increase in the trabecular vBMD was obtained by the DMAB group with 4.95%, followed by a non-significant increase of 3.39% in the PTH group and AL with a significant increase of 2.9%.

Interestingly, the PTH obtained a cortical strain decreased while the vBMD decrease, aspect not seen for the other treatments. The lowest strain decrease in the trabecular bone was given by PTH group with 4.15%. Then, AL and DMAB showed a significant decrease of 6.43% and 7.67%, respectively. All these reductions lead to the cortical bone having the smallest changes but still, presented MPE significant decreases in DMAB and AL groups. The trabecular area was the most affected in NAÏVE's group, showing a vBMD loss of 1.54% and a strain increase of 3.82%.

4.3 Zone Analysis

Treatment	Zone	vBMD	MPE
AL	Neck	+1.605*	-2.636
	Trochanter	+2.061*	-6.425*
DMAB	Neck	+2.540*	-5.503*
	Trochanter	+3.412*	-7.666*
PTH	Neck	+0.715	-4.145
	Trochanter	+0.443	-3.385
NAIVE	Neck	-1.099	+5.601
	Trochanter	-1.116	+3.788

Table 5: Relative difference in percentage divided by zone

Table 5. shows the changes in vBMD and MPE by zone. In the trochanter zone, vBMD significant increases were obtained by DMAB and AL individuals with 3.41% and 2.06%, correspondingly. The trochanter had the highest significant decrease in MPE too, provided by the same groups with 7.67%, and 6.43% of strain reduction. DMAB and AL also showed significant increases in the neck's vBMD, while significant decreases in MPE values of the neck were only shown by the DMAB group. On the other hand, the neck area presented higher changes in PTH patients with a 0.72% of density increase, and a 4.15% of strain decrease. Otherwise, the trochanter zone presented a vBMD decrease of 1.12% in NAÏVE patients while a 5.60% MPE increase in the neck. Showing an opposite behavior compared to treatment groups.

4.4 Zone and Tissue Analysis

Tables 6 and 7 present the strain and density changes by zone and tissue. In general, the most remarkable difference was presented in the Trochanter-Trabecular area. The highest significant increase in density in the area was provided by the DMAB group with 6.80%, followed by AL with 3.72%. Significant decreases in strain in this zone were provided by the same groups with 7.70% and 6.51%, respectively. Yet, the zones Neck-Trabecular, Neck-Cortical, and Trochanter-Cortical showed significant decreases in strain for DMAB, while AL just presented a significant decrease in the Trochanter-Cortical area. On the other hand, the Neck-Trabecular was more affected by PTH with 4.56% higher density and 4.91% less deformation. Finally, a decrease in the density of 1.87% in the Trochanter-Trabecular was shown for the NAÏVE group while an increase in the strain of 6.5% in the Neck-Trabecular.

Treatment	Neck/	vBMD	MPE
AL	Trabecular	+2.737*	-2.808
	Cortical	+1.083	-2.144
DMAB	Trabecular	+4.356*	-5.727*
	Cortical	+1.673	-4.868*
PTH	Trabecular	+4.561*	-4.905
	Cortical	-1.063	-1.869
NAIVE	Trabecular	-1.800	+6.502
	Cortical	-0.702	+3.340

Table 6: Relative difference in percentage divided by neck zone and tissue

Treatment	Trochanter/	vBMD	MPE
AL	Trabecular	+3.721*	-6.513*
	Cortical	+1.267	-4.921*
DMAB	Trabecular	+6.799*	-7.699*
	Cortical	+1.791	-7.151*
PTH	Trabecular	+3.639	-3.536
	Cortical	-1.119	-1.000
NAIVE	Trabecular	-1.866	+3.856
	Cortical	-0.665	+2.823

Table 7: Relative difference in percentage divided by trochanter zone and tissue

5 Discussion

This study was focused on the evaluation of different treatment efficacy with a DXA-based 3D FEM. Previous works [6] had focused on the analysis of osteoporosis pharmacological treatments efficacy by reporting strength changes. Still, it is important to deeply understand the drug behavior within the human body by focusing on how affects the biomechanical response in different parts of the bone. This patient-specific 3D finite element simulation allows an enhancement and enables going one step further to truly comprehend the drug's effectiveness. Such analysis allows the assessment of the drug's effect from integral bone to specific zone and tissue.

The two variables MPE and MPS were extracted from the biomechanical simulation to quantify this evaluation. Nonetheless, the stress parameter showed a non-expected response. Following the empirical relationships between vBMD and stiffness if the density is reduced so it will be the stiffness. Also, according to Hooke's Law, as the stiffness increases, the stress response will increase as well, producing a

stiffer material. In this sense, results points different, indicating that the stress may be affected by different factors. The lack of homogeneity of the tissue may cause certain areas to be more reinforced or overloaded than others. Besides, the fact of using mean values may cover the exact effect of the drug. Suggesting that the real biomechanical response is not effectively represented with MPS due to local effects that are not well captured when calculating mean values.

On the other hand, MPE is capable of analyzing more detailed bone reinforcement due to treatment. In this simulation, the bone material is linear-elastic, thus if its density increases, the strain decreases since it is inversely proportional to the stiffness. The reduced MPE represents that bone can resist better the load supported by becoming reinforced. In this study, the strain showed the expected biomechanical response along with treatments. The same areas where the density increase the most are the ones with less deformation produced.

Overall, the increase of the density and the decrease in the strain with the treatments show an enhancement, even more, when compared to the NAÏVE group that presented the opposite behavior. The highest improvements in Integral bone for both vBMD and MPE were obtained by the DMAB group.

The trabecular bone obtained higher outcomes than the cortical in both density and strain, for all treatments. But the most important enhancement in MPE was obtained by the DMAB group. Reasonable and consistent according to literature [25] which showed that the highest vBMD changes in the trabecular tissue were acquired with DMAB. Moreover, the maximum decrease in the strain in this tissue and group corroborates this statement.

Although the results showed that the trabecular obtained higher results in all treatments, theoretically the cortical bone should be reinforced the most with DMAB and AL. Still, these groups enhanced both tissues, but the MPE decrease in the trabecular bone is notable compared to cortical. This could be, as explained in prior literature [26][27], DXA technology showed difficulties in capturing well differences in the effect of the antiresorptive drug, such as AL and DMAB. Besides, the interconnectivity of the bone induces the incrementation in both tissues even though it is supposed to exhibit better results in the cortical compartment.

On the other hand, PTH is supposed to reinforce on a higher scale the trabecular bone, which was presented indeed while the cortical section only presents density decreases, as in the aforementioned works [26]. But still, presenting MPE decreases in both tissues being the trabecular the highest. This occurs since the bone manner acts as a whole. Both trabecular and cortical tissue are interconnected in conjunction, if a treatment enhances the biomechanical behavior of one tissue, it will directly affect the other by modifying the bone interface. Suggesting that the treatments are able to have a significant influence on femoral strength, even though it acts better on an specific compartment.

PTH showed a lower decrease of MPE than AL at the trabecular, contradicting literature [26] where PTH obtained higher strength changes. It could be due to the number of participants in this group, which was the smallest in the study. Also, by the reaction of the drug in these individuals, among other possibilities. This may directly affect the variability when calculating the mean.

As expected, the NAÏVE group showed opposite results to the treatment groups indicating what might happen to a patient that does not take any treatment. The trabecular area was the most affected by these patients. Reasonable considering the structure and porous of this compartment that loses density more easily by increasing the number and size of cavities in the tissue.

The trochanter zone was more reinforced than the neck. Most remarkable MPE differences were obtained by DMAB patients, but so were obtained notable improvements from AL individuals. This makes sense since it is the less affected area in this biomechanical study. Otherwise, the neck zone was the most affected due to the type of simulation performed, specifically on NAÏVE patients with higher bone mass loss. For a femur, a side-fall is the worst scenario in which a neck can be submitted being difficult to withstand an applied force. Even though, PTH stands out for reinforcing more this area. Being the only group that shows a higher improvement in the neck than in the trochanter region. Suggesting that this treatment would be the best fit for patients with a high neck fracture risk, which is the most common with most severe complications.

There is no previous literature with which the results can be compared due to the detailed level of information that comes from observing by zone. In the same way, when going into a deeper analysis with zone and tissue.

Getting more in detail, Trochanter-Trabecular zone stood out for its decreased strain values in DMAB individuals, being the highest improvement in the whole study. While the Trochanter-Cortical showed a significant decrease in MPE with DMAB even though had a slight increase in vBMD. AL followed an equal reinforcement behavior as DMAB in the same areas. Leading to the Neck-Cortical with the lowest improvements in DMAB and AL groups. Otherwise, the Neck-Trabecular was the most reinforced in PTH patients, while the Trochanter-Cortical presented the lowest enhancements in this treatment group. Suggesting that potentially DMAB would be the optimal treatment for a patient who needs a general reinforcement in their bones to avoid mass loss and fractures.

On the other hand, The Neck-Trabecular also showed a noteworthy deformation percentage in NAÏVE patients. Rationale when focusing on the most affected zone by the side-fall simulation. Considering that the NAÏVE group had no pharmacological treatment to help them fight osteoporosis it is normal to discover a degradation in the bone mass and density, producing more serious deformations and fracture risk. Exposing that an osteoporosis patient with no pharmacological treatment might easily break their bones by suffering from an impact, having minimum

stress applied, or even doing daily activities.

As any computational study, there are some limitations. The definition of the neck and the trochanter is an approximation. The selection of the critical zone was based only on anatomy references. It has been reported in literature [30] that the selection of the analysis zone is very important for fracture classification. This may also influence the evaluation of drugs. The number of patients in the cohort is small. A larger number of patients is necessary for the extrapolation of the results obtained in our study. Still, the current number of patients is in line with others reported in the literature [26]. The mesh of the model needs to be improved. The mesh presents sharp angles in critical load areas as in the neck. Smooth mesh is needed to improve quantitative results. Yet the overall tendency observed with the current model might not be significantly altered by the mesh. Mean values for evaluation might mislead the interpretation of the results. Local analysis for a group of elements significantly different would provide a more accurate vision of the effect of the drugs. The fall simulation replicates an experimental setup. However, the impact of the femur on the floor presents multiple angles of force application and impact with the surface. Yet, such setting helps to compare with other works of the literature and test the power of analysis by tissue, zone, and zone-tissue.

Despite everything, treatment patients presented important results showing an improvement compared to individuals without any medical therapies. All this demonstrates the importance of analyzing on a deeper level the effect of pharmacological treatments in different zones with biomechanical parameters and not only focusing on strength changes. Results indicate the major capability and potential of DXA-based 3D FEM simulations which manages to match the capacity and performance of the QCT: being cheaper, faster, and with less radiation. Corroborating how effective is this approach for osteoporosis diagnosis and drug treatment monitoring.

6 Conclusion

DXA-based 3D models were used to evaluate three different treatments. To the extent known, this is the first time that 3D DXA models have been used to address drug efficacy. The major principal strain was the FE-derived parameter that better-captured treatments effect. Trabecular bone was positively affected by all treatments. While DMAB and AL reinforced the trochanter area, PTH improved the mechanical response at the neck. Such information can help in understanding which would be the best osteoporotic treatment depending on the necessity of the patient. Moreover, complementing the standard two-dimensional DXA acquisition with a three-dimensional Finite Element Model focusing on biomechanical responses can assist, support, and analyze in short term the treatment's efficacy with patient-specific criteria. Much new insight has been acquired in order to prescribe evidence-based and reliably allowing the enhancement of outcomes in personalized medicine.

7 Future Work

Regarding future work, it would be interesting to perform a local analysis in each zone and bone tissue to better understand the effects of the drugs. Focusing on the important areas of studies such as the femoral neck, trochanter, cortical and trabecular bone. A larger database, including a match between gender, should be used to better extrapolate del results obtained in this thesis. Different load conditions could be further explored. Also, statistical models could be used to identify the elements with significant differences and analyze the effect of the drug on those specific elements.

Bibliography

[1] Guzon-Illescas O. Perez Fernandez E. Crespí Villarias N. et al. "Mortality after osteoporotic hip fracture: incidence, trends, and associated factors". In: *Journal of Orthopaedic Surgery and Research* 14.23 (2019). DOI: https://doi.org/10.1186/s13018-019-1226-6.

[2] Sociedad Española de Geriatría y Gerontología. *En españa la osteoporosis afecta a 3.5 millones de personas*. URL: https://www.segg.es/institucional/2017/02/23/en-espa%5C%C3%5C%B1a-la-osteoporosis-afecta-a-3-millones-y-medio-de-personas. (accessed: 15.10.2021).

[3] IOF International Osteoporosis Foundation. *Key statistic for Europe: International Osteoporosis Foundation*. URL: https://www.osteoporosis.foundation/facts-statistics/key-statistic-for-europe. (accessed: 19.03.2022).

[4] Radiological Society of North America. *Examen de densidad ósea (DEXA o DXA)*. URL: https://www.radiologyinfo.org/es/info/dexa. (accessed: 15.10.2021).

[5] Yang L. Palermo L. Black D. M. Eastell R. "Prediction of incident hip fracture with the estimated femoral strength by finite element analysis of DXA scans in the study of osteoporotic fractures". In: *Journal of Bone and Mineral Research* 29.12 (2014). DOI: https://doi.org/10.1002/jbmr.2291.

[6] Keaveny T. M. Hoffmann P. F. Singh M. Palermo L. Bilezikian J. P. Greenspan S. L. & Black D. M. "Femoral bone strength and its relation to cortical and trabecular changes after treatment with PTH, alendronate, and their combination as assessed by finite element analysis of quantitative CT scans." In: *Journal of Bone and Mineral Research* 23.12 (2008), pp. 1974–1982. DOI: https://doi.org/10.1359/jbmr.080805.

[7] Cannarella R. Barbagallo F. Condorelli R. A. Aversa A. La Vignera S. Calogero A. E. "Osteoporosis from an endocrine perspective: The role of hormonal changes in the elderly". In: *Journal of Clinical Medicine* 8.10 (2019). DOI: https://doi.org/10.3390/jcm8101564.

[8] Morgan E. F. Barnes G. L. Einhorn T. A. "Osteoporosis". In: *The Bone Organ System* 3.20 (2013). DOI: https://doi.org/10.1016/b978-0-12-415853-5.00001-7.

[9] Boskey A. L. "Bone composition: Relationship to bone fragility and antiosteoporotic drug effects". In: *Bonekey Rep* 2.447 (2013). DOI: https://doi.org/10.1038/bonekey.2013.181.

[10] Monier-Faugere M.-C. Chris Langub M. Malluche H. H. *Bone Biopsies: A modern approach. Metabolic Bone Disease and Clinically Related Disorders*. Third Edition. Academic Press, 1998, pp. 237–273. DOI: https://doi.org/10.1016/b978-012068700-8/50009-8.

[11] N. Hambli R. Hattab. "Application of neural network and finite element method for multiscale prediction of bone fatigue crack growth in cancellous bone". In: *Multiscale Computer Modeling in Biomechanics and Biomedical Engineering* 3.30 (2012). DOI: https://doi.org/10.1007/8415_2012_146.

[12] Guede D. González P. Caeiro J. R. "Review of Biomechanics and bone (1): Basic concepts and classical mechanical trials. Revista de Osteoporosis y Metabolismo Mineral". In: *Revista de Osteoporosis y Metabolismo Mineral* 5.1 (2013), pp. 43–50. DOI: https://dx.doi.org/10.4321/S1889-836X2013000100008..

[13] S. Robertson. *What are osteoblasts?* URL: https://www.news-medical.net/health/What-are-Osteoblasts.aspx. (accessed: 07.06.2022).

[14] M. van Oostwaard. "Application of neural network and finite element method for multiscale prediction of bone fatigue crack growth in cancellous bone". In: *Perspectives in Nursing Management and Care for Older Adults* 1.13 (2018). DOI: https://doi.org/10.1007/978-3-319-76681-2_1.

[15] iSanidad. *La osteoporosis a Nivel Mundial produce una fractura ósea Cada Tres segundos*. URL: https://isanidad.com/98748/la-osteoporosis-a-nivel-mundial-produce-una-fractura-osea-cada-tres-segundos/. (accessed: 12.10.2021).

[16] van Oostwaard M. "Osteoporosis". In: *The Bone Organ System* 3.20 (2018). DOI: https://doi.org/10.1016/b978-0-12-415853-5.00001-7.

[17] Fischer S. J. Gray J. L. *Hip fractures*. URL: https://orthoinfo.aaos.org/en/diseases--conditions/hip-fractures. (accessed: 07.06.2022).

[18] Mayo Foundation for Medical Education and Research. *Osteoporosis*. URL: https://www.mayoclinic.org/es-es/diseases-conditions/osteoporosis/symptoms-causes/syc-20351968. (accessed: 22.12.2021).

[19] J. Iwamoto. "Hip fracture protection by alendronate treatment in postmenopausal women with osteoporosis: A review of the literature". In: *Clinical Interventions in Aging* 3.3 (2008), pp. 483–489. DOI: https://doi.org/10.2147/cia.s3177.

[20] Wikipedia Foundation. *Bifosfonato*. URL: https://es.wikipedia.org/wiki/Bifosfonato. (accessed: 15.01.2021).

[21] C. C.(n.d.) Cancer. *Denosumab*. URL: https://chemocare.com/es/chemotherapy/drug-info/denosumab.aspx. (accessed: 28.12.2021).

[22] Agencia Española de Medicamentos y Productos Sanitarios. *Denosumab. Riesgo de Osteonecrosis Mandibular e hipocalcemia*. URL: https://www.aemps.gob.es/informa/notasinformativas/medicamentosusohumano-3/seguridad-1/2014/ni-muh_fv_13-2014-denosumab/. (accessed: 30.12.2021).

[23] Gallagher J. C. Genant H. K. Crans G. G. Vargas S. J. Krege J. H. "Teriparatide Reduces the Fracture Risk Associated with Increasing Number and Severity of Osteoporotic Fractures". In: *The Journal of Clinical Endocrinology Metabolism* 90.3 (2005), pp. 1583–1587. DOI: https://doi.org/10.1210/jc.2004-0826.

[24] Eli Lilly and Company 2022. *Forsteo® (Teriparatida): Mecanismo de Acción*. URL: https://www.lillymedical.eu/es-es/answers/forsteo-teriparatida-mecanismo-de-acci-n-40982. (accessed: 30.12.2021).

[25] Winzenrieth R. Humbert L. Di Gregorio S. Bonel E. García M. Del Rio L. "TEffects of osteoporosis drug treatments on cortical and trabecular bone in the femur using DXA-based 3D modeling". In: *Osteoporosis International* 29.10 (2018), pp. 2323–2333. DOI: https://doi.org/10.1007/s00198-018-4624-4.

[26] Keaveny T. M. Donley D. W. Hoffmann P. F. Mitlak B. H. Glass E. V. San Martin J. A. "Effects of teriparatide and alendronate on vertebral strength as assessed by finite element modeling of QCT scans in women with osteoporosis". In: *Journal of Bone and Mineral Research* 22.1 (2006), pp. 149–157. DOI: https://doi.org/10.1359/jbmr.061011.

[27] Faulkner K. G. "Bone matters: Are density increases necessary to reduce fracture risk?" In: *Journal of Bone and Mineral Research* 15.2 (2010), pp. 183–1870. DOI: https://doi.org/10.1359/jbmr.2000.15.2.183.

[28] Ruiz Wills C. Olivares A. L. Tassani S. Ceresa M. Zimmer V. González Ballester M. A. del Río L. M. Humbert L. Noailly J. "3D patient-specific finite element models of the proximal femur based on DXA towards the classification of fracture and non-fracture cases." In: *Bone* 121 (2019), pp. 89–99. DOI: https://doi.org/10.1016/j.bone.2019.01.001.

[29] Orwoll E. S. Marshall L. M. Nielson C. M. Cummings S. R. Lapidus J. Cauley J. A. Ensrud K. Lane N. Hoffmann P. R. Kopperdahl D. L. Keaveny T. M. "Finite element analysis of the proximal femur and hip fracture risk in older men." In: *Journal of Bone and Mineral Research* 24.3 (2009), pp. 75–483. DOI: https://doi.org/10.1359/jbmr.081201.

[30] Ruiz Wills C. Tassani S. Di Gregorio S. Martínez S. González Ballester M. A. Humbert L. Noailly J. Río L. M. D. "Relative fragility of osteoporotic femurs assessed with DXA and simulation of finite element falls guided by emergency X-rays". In: *Revista De Osteoporosis y Metabolismo Mineral* 12.2 (2020), pp. 62–70. DOI: DOI:http://dx.doi.org/10.4321/S1889-836X2020000200005.