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A predictive mechanical model for evaluating vertebral fracture probability in lumbar spine under different osteoporotic drug therapies

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ABSTRACT

Osteoporotic vertebral fractures represent a major cause of disability, loss of quality of life and even mortality among the elderly population. Decisions on drug therapy are based on the assessment of risk factors for fracture from bone mineral density (BMD) measurements.

A previously developed model, based on the Damage and Fracture Mechanics, was applied for the evaluation of the mechanical magnitudes involved in the fracture process from clinical BMD measurements. BMD evolution in untreated patients and in patients with seven different treatments was analyzed from clinical studies in order to compare the variation in the risk of fracture. The predictive model was applied in a finite element simulation of the whole lumbar spine, obtaining detailed maps of damage and fracture probability, identifying high-risk local zones at vertebral body.

For every vertebra, strontium ranelate exhibits the highest decrease, whereas minimum decrease is achieved with oral ibandronate. All the treatments manifest similar trends for every vertebra. Conversely, for the natural BMD evolution, as bone stiffness decreases, the mechanical damage and fracture probability show a significant increase (as it occurs in the natural history of BMD). Vertebral walls and external areas of vertebral end plates are the zones at greatest risk, in coincidence with the typical locations of osteoporotic fractures, characterized by a vertebral crushing due to the collapse of vertebral walls.

This methodology could be applied for an individual patient, in order to obtain the trends corresponding to different treatments, in identifying at-risk individuals in early stages of osteoporosis and might be helpful for treatment decisions.

Abbreviations: BMD, Bone Mineral Density; CT, Computed Tomography; DXA, Dual-energy X-ray Absorptiometry; FE, Finite Elements; FRAX, Fracture Risk Assessment Tool; L1 to L5, Lumbar vertebrae; PTH, Parathyroid Hormone; QCT, Quantitative Computed Tomography; S1, Sacrum; T12, Last thoracic vertebrae; WHO, World Health Organization.

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1. Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass and deterioration of bone microstructure, leading to bone fragility and susceptibility to fracture [1]. Currently, osteoporotic fractures are considered as an important public health problem leading to morbidity and mortality, generating very important economic costs [2]. Osteoporosis represents a major cause of disability, loss of quality of life and even death among the elderly population [3–6].

Osteoporosis is caused by a skeletal involution linked to aging, which is more prevalent in women: the lifetime risk for a fragility fracture at the age of 50 lies within the range of 40% in women [7]. Osteoporosis has been called the silent epidemic because in most cases the first symptom is the appearance of a first fragility fracture, so it is essential to establish treatment to prevent fractures. The decision to treat is based on the analysis of risk factors for fracture.

Vertebral fracture is the most common osteoporotic fracture, being more prevalent in women than in men [8,9], leading to back pain, kyphosis and severe functional and vital impact in 30–50% of patients [10,11]. Underdiagnosis of osteoporotic vertebral fracture is common for lack of complementary tests in older women who visit the doctor complaining of back pain and sometimes because the symptomatology of the first fracture is not evident [12,13].

Different publications estimate that only 40% of fractures are diagnosed [12,14]; other assessments estimate that only 5–20% of these vertebral fractures are diagnosed in primary care [15]. The first vertebral fracture is a factor of high risk of new fractures, localized in another vertebra or in other areas of the skeleton [16–20], leading to so-called fracture cascade [21] when new fractures occur in the spine. Decisions on drug therapy in osteoporotic patients without previous fractures are mainly based on the analysis of risk factors that predispose to fracture. A risk assessment tool called FRAX® (Fracture Risk Assessment Tool) has been developed by the World Health Organization (WHO) for this purpose [7,22–24]. The risk of major osteoporotic fractures (hip, vertebrae, humerus and wrist) over the next 10 years can be estimated with the FRAX® tool. The probability of fracture is calculated on the basis of age, body mass index and several dichotomized variables (previous fracture, smoking, rheumatoid arthritis, etc.). Other studies have questioned the effectiveness of FRAX® as a tool for predicting fracture risk [25–28].

Several previous surveys have assessed the risk of fracture using various methodologies, but mostly based on BMD measurements [29,30], which is considered to be the most important indicator of diagnosis of osteoporosis and monitoring treatment [31]. BMD measurements have also been used to determine the mechanical strength [32] or to develop statistical models for predicting the risk of fracture [29,30,33–35].

The treatment of osteoporosis includes general measures (breaking harmful habits, proper nutrition, physical exercise and prevention of falls, intake of Calcium and Vitamin D) and pharmacological treatment. The drugs used today are cost-effective [36]. Various medications are available for prevention and treatment of osteoporosis. Pharmacologic interventions preventing fractures in patients with osteoporosis aim at correcting the bone remodeling imbalance by either reducing bone resorption and bone turnover or stimulating bone formation and strontium ranelate, both inhibit bone resorption and stimulate bone formation, which gives a mixed effect [37,38]; this last drug is approved in Europe but not in the USA. The fundamental aim of pharmacological treatment is to increase BMD, reducing resorption and bone turnover or stimulating bone formation, but not all drugs have the same effect and the increase percentages in BMD are different.

In the field of Finite Element (FE) simulation, different models and methodologies were used for predicting bone strength or fracture risk at different ages and locations. Lee et al. [19] present a micromechanical model of bone behavior, which is difficult to extrapolate to the scale required to get realistic predictions. Boccaccio et al. and Zhang et al. [39,40] develop more advanced macro-mechanical models, analyzing a complete functional unit of the spine in terms of mechanical behavior depending on bone density. MacNeil et al. [41] build a 2D model in the sagittal plane, using bone geometry and BMD measurements obtained from radiographs and Dual-energy X-ray Absorptiometry (DXA), calculating the stiffness in terms of patient's age. For proximal femoral fractures, Kaneko et al. [42] develop a model based on imaging techniques, establishing a statistical correlation between the prediction of bone strength and the risk of osteoporotic fracture. A different methodology is applied by Bryan et al. [43], who suggest a parametric model incorporating both the geometry and the properties of bone. A similar methodology is used by Bessho et al. [44], with a parametric analysis concerning load and support conditions. Some authors have begun to incorporate yield criteria for fracture risk prediction, as Derikx et al. [45] who apply the Drucker–Prager criterion on a model made from Quantitative Computed Tomography (QCT), with asymmetric yielding in tension and compression. In a similar way, Tellache et al. [46] apply an anisotropic yield criterion on a model constructed from Computed Tomography (CT) for the prediction of fracture risk. With a different approach, Amin et al. [47] performed a comparative analysis of fracture risk predictions based on BMD measurements against those ones obtained from an FE model developed from QCT. Finally, on the matter of drug treatments, Keaveny et al. [48] analyze the influence on bone strength of Parathyroid Hormone (PTH) and alendronate, using a FE model developed from QCT scans of osteoporotic patients.

Currently, the most popular clinical tool for fracture risk assessment is FRAX®, which does not consider bone strength as a relevant magnitude. All the aforementioned computational methods use clinical or mechanical magnitudes related to bone fracture in an independent way, without considering their mutual influence, as actually happens.

The aim of this work is to apply a numerical model, previously developed [49], in predicting the risk of osteoporotic vertebral fractures based on the Damage Mechanics and Fracture Mechanics, both for the natural BMD evolution and for seven different treatments in order to compare the variation in the risk of fracture. The proposed model allows establishing direct relationships between clinical and mechanical magnitudes, so evolution of BMD, bone strength, damage and fracture probability can be simultaneously evaluated at any age from the initial measurements of BMD. It is not intended to replace the models based solely on BMD, but to complement