

## EVALUATION OF BONE MECHANICAL STRENGTH AND FRACTURE RISK ASSESSMENT [FRAX®] IN PATIENTS WITH HIP JOINT REPLACEMENT SURGERY

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### Abstract

**Background:** Fracture risk assessment tools are useful to calculate the long term probability of osteoporotic fracture. However, how it reflects bone quality is unknown. The aim of this study was to correlate the FRAX® tool with bone mechanical properties.

**Methods:** Six patients submitted to hip replacement surgery, either due to osteoporotic fractures or to osteoarthritis, were evaluated. Bone samples were collected and the mechanical properties assessed by compression tests. Patients' data regarding the presence of clinical risk factors for fracture were registered. Laboratorial assessment of bone metabolic parameters and a dual X-ray absorptiometry (DXA) were done.

**Results:** Analysis of the load-displacement curves showed that patients with fragility fractures (n=4) had low values of elastic modulus, yield load and energy absorbed until yield point. Osteoarthritis patients tend to have a better biomechanical performance. Femoral neck DXA scan was also performed in 3 patients. Fragility fracture patients had a lower bone mineral density than the patients with osteoarthritis. FRAX® algorithm was applied and a positive relation was found between FRAX® results and biomechanical parameters. Blood bone metabolic markers were within the normal range for all the subjects.

**Conclusions:** The worse mechanical properties observed in the fragility fracture patients were related to high probability of fracture given by FRAX®. These observations, in a very small sample, need further confirmation. However, they suggest that the fracture risk assessment tool, FRAX®, may reflect the current mechanical bone behavior of the patient.

**Keywords:** Mechanical Tests; Osteoporosis; Hip Fracture; Fragility Fracture; FRAX®.

### Introduction

Osteoporosis (OP) is defined as a systemic skeletal disease, characterized by low bone mass and microarchitectural deterioration with a resulting increase in bone fragility and, hence, susceptibility to fracture.<sup>1</sup> Osteoporotic fractures, namely hip fractures, impose a major economic burden on health-care systems.<sup>2</sup> Globally, OP affects around 150 million people<sup>3</sup> and in Europe it affects about 75 million persons.<sup>4</sup> The *Third National Health and Nutrition Examination Survey* (NHANES III) study performed in United States of America, revealed that 20% of post-menopausal Caucasian women, 12% of Hispanic women and 8% of African American women, have OP.<sup>5</sup> In Portugal, the incidence of hip fractures caused by low or moderate impact falls in women varies from 154 to 572 per 100 000 inhabitants, while in men the incidence is lower and varies from 77 to 232 per 100 000 inhabitants.<sup>6-8</sup>

Currently, the standard diagnostic tool for osteoporosis is Dual X-ray Absorptiometry (DXA) which only measures bone mineral density (BMD) and does not take into consideration the quality of bone, including its microarchitectural and structural design. The assessment of osteoporosis by BMD alo-

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ne underestimates the risk of having an osteoporotic fracture. For example, the annual incidence of hip fracture increases approximately 30 fold between 50-90 years but this is out of proportion to what would be expected by computing the fracture risk associated with the loss of bone that would occur during this 40 years time frame (only a 4 fold increase in fracture risk).<sup>2</sup> Although bone mass is an important component of the fracture risk, other abnormalities in bone structure contribute to fragility.

The strength of bone is determined by its composition and structure. It must be stiff, flexible and light.<sup>9</sup> Bone is a composite structure composed mainly by type I collagen and calcium hydroxyapatite crystals.<sup>10</sup> The increase in tissue mineral density potentiates bone stiffness but sacrifices flexibility. On the other hand, newly formed collagen gives flexibility to the bone but decreases stiffness. The composition and degree of collagen cross-linking also influence the mechanical performance.<sup>11,12</sup> However, the occurrence of fracture depends on many aspects like the propensity to falls, energy of impact, bone size and not only on bone biomechanical proprieties and microarchitecture.<sup>13-16</sup> A computer-based algorithm, FRAX<sup>®</sup>, has recently been developed by the University of Sheffield in order to assess the ten year probability of fracture, taking into account clinical and epidemiological risk factors, as well as DXA results. The clinical risk factors include low body mass index, prior low-energy fracture, parental history of hip fracture, long term use of oral glucocorticoids, rheumatoid arthritis and other secondary causes of osteoporosis, current cigarette smoking and alcohol intake. The ten year fracture probability calculated by FRAX<sup>®</sup> depends on the fracture rate of each country. At the moment, interventional thresholds are being developed based on cost-effectiveness analysis of each country in order to allow the direct application of this methodology to clinical practice.<sup>2,17</sup> However, a direct link between the fracture risk assessment at 10 years obtained by the FRAX<sup>®</sup> tool and the bone biomechanical properties at the moment of the evaluation would further contribute to refine the correct threshold for treatment decision based not only on epidemiological cost-effectiveness analysis but also on physiopathological and clinical data.<sup>18</sup>

Therefore, the aim of this exploratory study was to correlate the individual ten year probability of fracture, based on clinical fracture risk factors and DXA results, with bone mechanical properties.

## Material and methods

### Study population

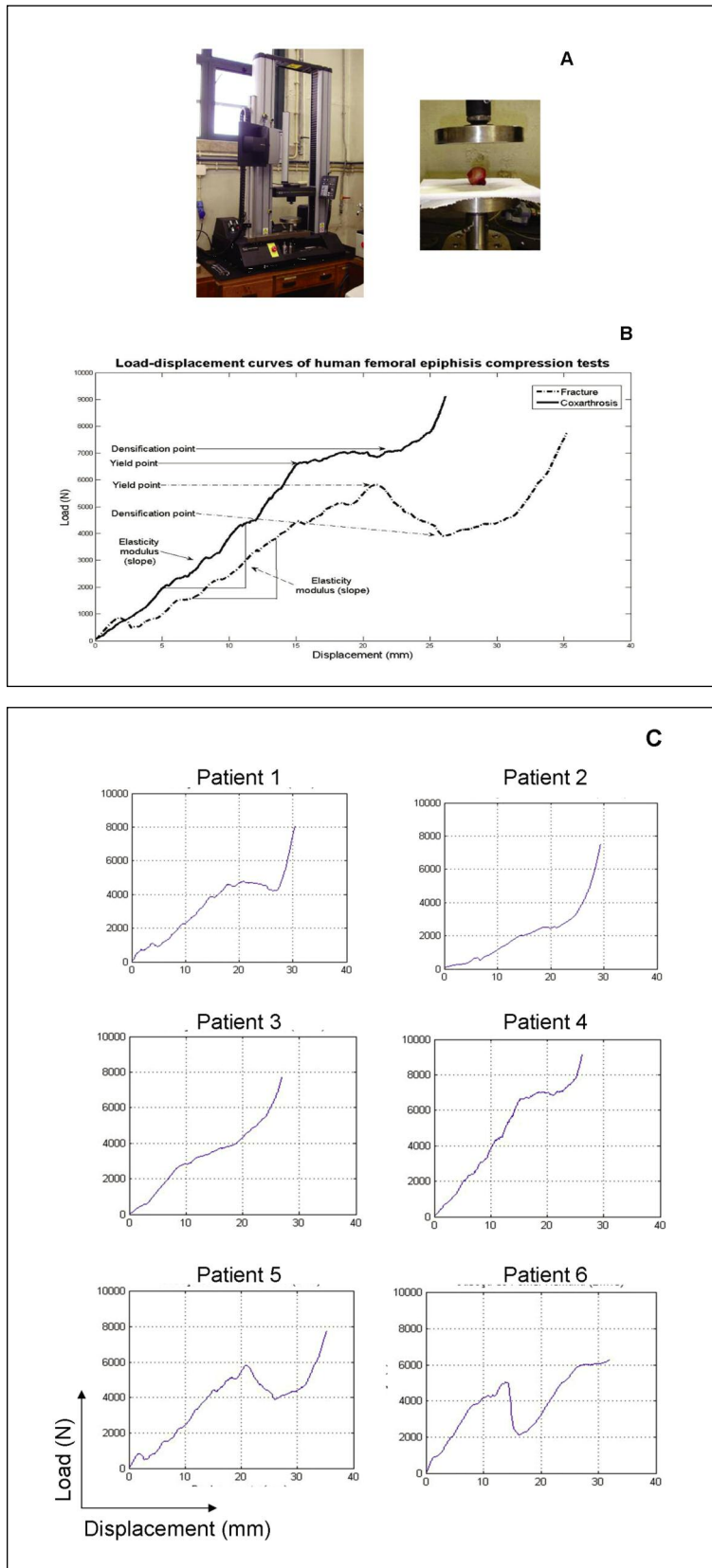
Patients submitted to hip replacement surgery, either due to osteoporotic fractures or to osteoarthritis, were evaluated. Laboratorial parameters of bone metabolism, such as bone alkaline phosphatase (ALP), bone specific alkaline phosphatase (BSALP), procollagen type 1 N-terminal propeptide (P1NP), collagen type 1 beta C-terminal telopeptide (b-CTX), serum calcium and phosphorus and parathormone levels, were assessed. Femoral neck BMD was measured by DXA scan using a Lunar Prodigy densitometer (GE Healthcare, United Kingdom) and t score results were calculated using NHANES reference values for women aged 20-29 years.

Risk factors for fracture were obtained from a clinical protocol – age, sex, low body mass index ( $BMI \leq 19 \text{ kg/m}^2$ ), prior fragility fracture, parental history of hip fracture, long term use of oral glucocorticoids (eg. for 3 months or more), rheumatoid arthritis and other secondary causes of osteoporosis, current smoking and alcohol intake (3 or more units/day). The probability of fracture at ten years was predicted using the FRAX<sup>®</sup> tool available online (<http://www.shef.ac.uk/FRAX/>), calibrated to the epidemiology of fracture and life expectancy of Spain, since in Portugal this data was not available. The algorithm provides two outputs, the ten year probability of having a major osteoporotic fracture (clinical spine, hip, forearm or humerus) and the ten year probability of a hip fracture alone.

### Mechanical tests

At the time of surgery, proximal femoral samples were collected and stored at  $-80^\circ\text{C}$ . Samples were defrosted at room temperature before testing.

Compression tests on femoral epiphysis were performed in a universal testing machine (Instron 5566<sup>TM</sup>, Instron Corporation, Canton, USA) using a load cell of 10kN (Figure 1A). The biomechanical strength variables were displayed from the load-displacement curves (Figure 1B) obtained with the *Bluehill 2 Software* (Instron, Copyright 1997-2007) and analyzed using *MatLab 7.1* software (R14 SP3, The Mathworks, Inc, Copyright 1984-2006). The software has the ability to build stress-strain representations from load-displacement points once initial dimensions are provided for each specimen. In this test, a cross head speed of 0.1mm/s was used and elasticity modulus, yield load and energy until yield point were obtained.



## Results

### Study population and clinical risk factors for fracture

Six patients submitted to hip replacement surgery were evaluated for clinical risks factors for fracture. Five patients were women and one was a man. The arthroplasty was performed in four patients due to low energy trauma and in the other two because of osteoarthritis (Table I). All patients with a fragility fracture had between one to three clinical risk factors. Patient number one was under systemic corticosteroid therapy for several years due to asthma. Patient number two had terminal chronic renal failure since 2006. Patient number 3 had several spine osteoporotic fractures and patient 4 had simultaneously type 1 diabetes mellitus and tobacco habits. This last patient was under bisphosphonate treatment for several years. The patients submitted to hip replacement surgery due to osteoarthritis did not refer any clinical risk factor for fracture.

Femoral neck DXA scan was performed in 3 patients. Patients with fragility fracture had a lower bone mineral density than those

**Figure 1.** Experimental setup and load-displacement curves obtained after femoral head compression. Images of the testing machine and a human femoral head standing on the inferior plate of a compression test setup (A). Patient 1 and 5 load-displacement compression curve (B). Curves were obtained in order to determine the yield point = (yield displacement, yield load), or after calculations, the elastic modulus (slope of the curve between the origin and the yield point) and the energy until yield point (area under the graphic from the origin until the yield point, calculated using trapez

**Table I. Epidemiological and clinical characteristics of the patients and their clinical risk of fracture assessment**

	Femoral neck DXA								
	Diagnosis	Age (years)	Gender	BMI (Kg/m <sup>2</sup> )	scan		Clinical risk factors (n)	FRAX®	
					T score	BMD (g/cm <sup>2</sup> )		Major osteoporotic fracture (%)	Hip fracture (%)
Patient 1	FF	77	F	24.4	–	–	2	28.0	15.0
Patient 2	FF	67	F	24.6	-3.8	0.525	2	21.0	12.0
Patient 3	FF	86	F	20.4	–	–	1	26.0	15.0
Patient 4	FF	69	F	24.0	-2.0	0.738	3	11.0	4.7
Patient 5	OA	73	F	24.8	-1.6	0.673	0	5.4	1.4
Patient 6	OA	85	M	25.9	–	–	0	6.6	3.6

FF – Fragility fracture

OA – Osteoarthritis

**Table II. Values calculated from mechanical compression load-displacement curves of human femoral epiphysis**

	Diagnosis	Diameter (mm)	Elastic modulus (N/mm)	Yield load (N)	Densification load (N)	Energy until yield point (N/mm)	Energy until densification point (N/mm)
Patient 1	FF	41.87	240.7	4.602	4.237	39.465	80.603
Patient 2	FF	38.49	132.8	2.003	2.484	11.688	27.468
Patient 3	FF	41.18	319.8	2.842	4.927	13.804	59.818
Patient 4	FF	41.29	407.6	6.608	7.101	44.441	96.741
Patient 5	OA	43.13	287.5	5.826	4.571	58.939	104.210
Patient 6	OA	48.60	449.2	3.828	2.170	17.482	48.987

FF – Fragility fracture

OA – Osteoarthritis

with osteoarthritis (Table I).

Biochemical markers of bone turnover were within the normal range in all patients.

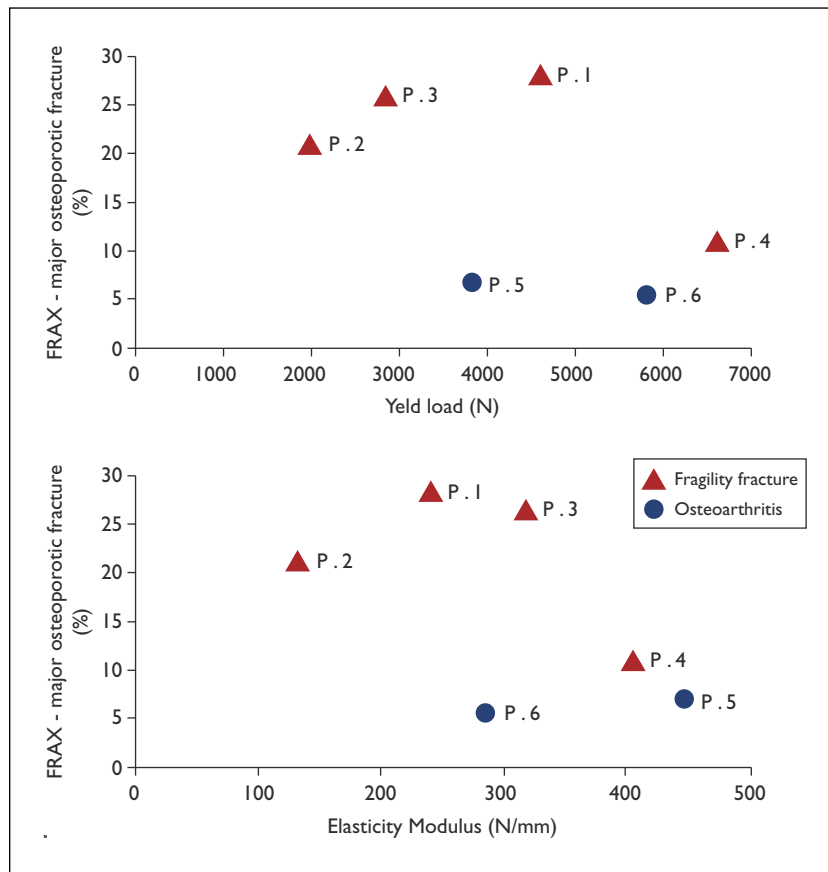
### Fracture risk assessment predicts mechanical bone behavior

Analysis of the load-displacement curves of patients submitted to hip replacement surgery was done. In this kind of curves the size of the femoral heads has an impact in the biomechanical behaviour. Osteoarthritic samples tend to have a larger diameter than femoral heads collected from fragility fractures, in the same way that men tend to have larger femoral epiphysis than women. So, in order to make a more accurate comparison, it was used the largest fragility fracture woman's femoral head (patient 1) and the smallest osteoarthritic (patient 5), where the difference in diameter is 1.27cm. These patients were both women and the

age difference was of 4 years. The analysis of the load-displacement curves (Figure 1B), from the femoral heads of patients 1 and 5, showed that the fragility fracture sample (Table II) had lower, elasticity modulus (reflecting reduced stiffness), yield load (meaning that a lower load was needed to cause the first microfractures and to start a plastic and definitive deformation of bone) and energy until yield point (that is, the energy that bone can support before fracture) than the osteoarthritic one.

Regarding the other femoral heads, with exception of the elastic modulus, the load and the energy absorbed until the yield point were higher in the osteoarthritic femoral heads than in the fragility fracture ones.

Patient number 4, who had a fragility fracture and was under bisphosphonate therapy, was an exception, revealing a better biomechanical per-



**Figure 2.** Relation between the ten years probability of having a major osteoporotic fracture given by FRAX® and the biomechanical parameters elastic modulus and yield load

formance than the others with fragility fracture.

The FRAX® algorithm was applied and the probability of hip fracture and the ten year probability of having a major osteoporotic fracture was determined in each patient (Table I) and then compared with biomechanical parameters (Figure 2). In fragility fracture patients FRAX® output was always above 20% (21-28%) with exception of patient 4 that had probability of having a major osteoporotic fracture of 11%. These patients had worst mechanical behaviour. Moreover, in this group patient 4 was the one that have the better mechanical performance along to the lower FRAX output, reinforcing the multifactorial mechanism of fracture. In Patients 5 and 6 (osteoarthritis) the risk of major osteoporotic fracture was of 6,6% and 5,4% respectively and they had good mechanical performance.

A positive relation was found between the results from FRAX® and the biomechanical param-

eters resulted from the compression tests. Patients with higher fracture risk were found to have poor biomechanical performance.

## Discussion

The fracture risk assessment tool – FRAX® – was developed at the Sheffield University, based in clinical risk factors for fractures identified in previous meta-analysis. It uses data from nine cohorts, including those from North America, Europe, Asia and Australia and it has been validated in eleven independent populations with similar geographic distribution.<sup>18</sup> The FRAX® tool calculates the ten year absolute risk for fracture and represents a step forward when compared to the relative risk provided by DXA measurements; it can have major implications in the future, with impact in pharmacoeconomic and clinical treatment decisions. Bone

properties, namely mechanical ones, depend on bone structure, which ultimately are influenced, through complex and not fully understood mechanisms, by clinical risk factors and bone mineral density, which are the variables required for the calculation of fracture risk probability by FRAX®. However, it is unknown how fracture risk computation by FRAX reflects bone quality and mechanical properties at the time of assessment, which is of major importance since the OP therapeutic interferes with bone quality.<sup>19-21</sup> This work, performed as an exploratory proof of concept approach, relates the ten year probability of fracture given by FRAX® with the deterioration of the quality of bone analysed by mechanical tests. Despite promising, this study has major limitations such as the sample size and the fact that the whole femoral head was used for the compression tests, which means that cortical, trabecular and water bone components were tested simultaneously which might have difficult data interpretation.<sup>22</sup> However, *in vivo*, load is applied on whole femoral head and indeed these factors influence the mechanical response in real life conditions. The problem is that femoral heads are neither homogeneous, nor perfect spheres with the same dimensions, which induces bias in the compression results and limits their reproducibility. Therefore, the lack of reproducibility does not allow us to have an accurate comparison between the two study groups. However, comparing patients 1 and 5, who have the most alike age and anatomic features, suggests that the biomechanical behaviour is worse for the patients that had a fragility fracture than for those with osteoarthritis.

This exploratory study allows us to sustain the hypothesis that FRAX® can have a correlation with mechanical properties and it is our view that this concept should be tested in a larger sample with mechanical tests performed in cylinders of trabecular bone extracted from the femoral epiphysis, which enables to calculate stress and strain and will allow to compare the mechanical results from different sample dimensions, thus, conducting to a higher reproducibility.

## Conclusion

The worse mechanical properties observed in the patients that sustained a fragility fracture were related with the higher probability of fracture

calculated by FRAX®. These observations, in a very small sample, need further confirmation. However, they suggest that the fracture risk assessment tool FRAX® may reflect bone mechanical behaviour.

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## VIII Jornadas do Aparelho Locomotor. Novos Desafios em Reumatologia

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