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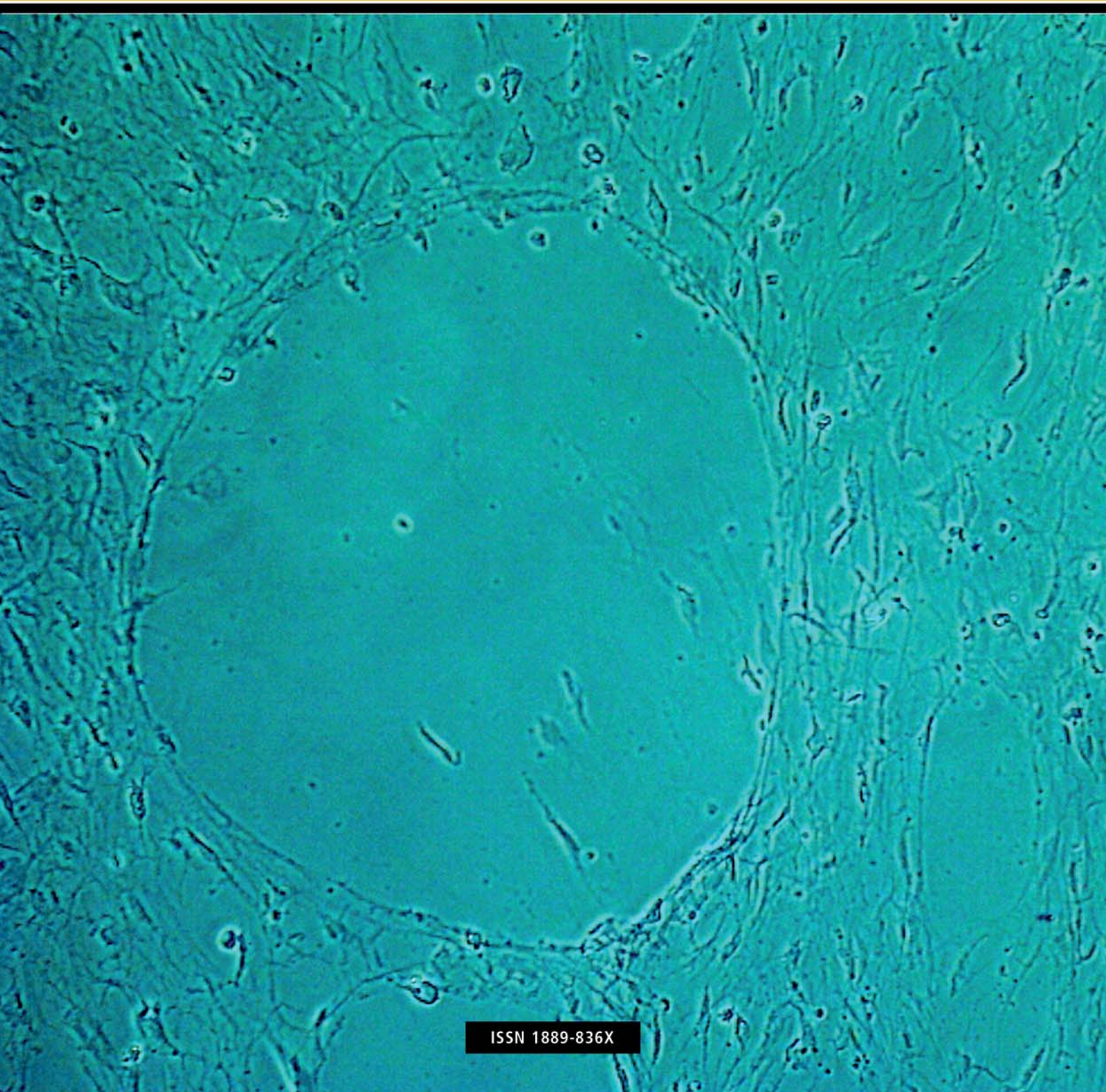

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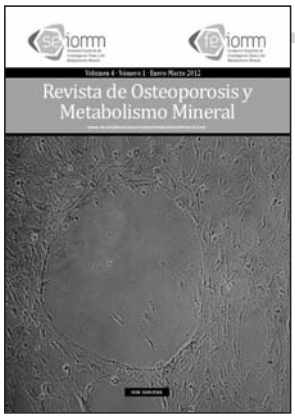

Our cover

Vessel formation from endothelial cells derived from the differentiation of mesenchymal stem cells from human bone marrow.

Authors:
Raquel Santiago Mora, Antonio Casado Díaz y José Manuel Quesada

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Diabetes mellitus type 2 and osteoporosis

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Osteoporosis and diabetes mellitus are two diseases with high prevalence which are associated with an increase in the risk of fragility fractures, and with a substantial impact on the morbidity and the mortality of the population in general. Although various observational studies have investigated the association between the two, the mechanism by which diabetes favours the appearance of fractures has not been properly established.

Most of the epidemiological studies carried out in patients with type 2 diabetes have shown an increase in bone mineral density[1], in spite of which there is an increased risk of fracture of 1.5 for hip fracture, proximal humerus and distal radius[2]. In terms of the risk of vertebral fracture, the results are less uniform, although most of the studies also show an increase in risk[3,4].

Hyperglycemia exerts both direct effects on bone cells, especially the osteoblasts, and indirect effects through the formation of products deriving from glycation.

In vitro, high levels of glycemia stimulate or inhibit osteoblast proliferation as a function of the phase of the cell cycle. The differentiation of these cells is especially suppressed, which is shown in the decrease in the production of osteocalcin, of the deposit of calcium and in bone mineralisation. The expression of the receptors for parathormone and vitamin D are also reduced. In addition, the hyperglycemia affects the functionality of the osteoblasts through the induction of an osmotic response mediated by its sensitivity to the acid medium induced by the lactate[5].

The hyperglycemia also changes the formation of the collagen fibres which reduces the formation of the extracellular protein matrix and the mineralisation. The advanced glycation end products (AGEs) are formed *in vivo* through the Maillard reaction, a reduction of glucose with proteins to form an unstable product which later stabilises, resulting in an irreversible non-enzymatic and posttranscriptional modification of the protein involved[6].

The high levels of AGEs and their accumulation play an essential role in the development of the complications associated with diabetes[7]. High levels of AGEs have been found in various tissues and have been related to low turnover of tissue in tendons, skin, amyloid plaques and cartilage. Their accumulation in the bone reduces the activity of the osteoblasts by the bonding of the AGE products with specific receptors (RAGE), alters osteoclastogenesis and reduces mineralisation. The collagen in the extracellular matrix modified by the AGEs is more difficult to eliminate by the hydrolytic enzymes, which increases bone fragility. The presence of AGEs also interferes in the interaction between the bone cells and the extracellular matrix[5]. Therefore, excess glycation may affect the properties of the bone, and this effect is evident above all in the cortex due to the accumulation of AGEs such as pentosidine in the parts of the skeleton with less rotation[8].

In addition, acute and chronic hyperglycemia has been shown to suppress the expression of the genes associated with the maturation of the osteoblasts in rats with diabetes[5]. As a counter to this, Miranda Diaz et al. in an article published in this number have demonstrated that the gene expression of RANKL, RANKL/OPG ratio and Runx2 are found to be altered in cultures of osteoblasts from diabetic patients with hip fracture, this being increased[9]. The authors postulate that these fin-

dings would mean a higher number of less differentiated osteoblasts with a higher expression of RANKL, which means that there would be a greater activation of osteoclastogenesis, a higher rate of remodelling and, therefore, a negative influence on bone resistance. However, histomorphometric studies in patients with diabetes have shown a low recruitment of osteoblasts along with a reduction in the rate of mineral apposition[10].

In short, to avoid glycation by controlling of hyperglycemia and the consequent reduction in AGEs should be the most effective tool to delay and minimise bone-related complications in diabetic patients.

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Gene study (OPG, RANKL, Runx2 and AGE receptors) in human osteoblast cultures from patients with type 2 diabetes mellitus and hip fracture. Influence of levels of glucose and AGEs

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Summary

Introduction: Diabetes mellitus (DM) type 2 is associated with a higher risk of osteoporotic fracture. Many factors have been indicated as possible mechanisms responsible for this, among which are changes in bone remodelling which may be induced by variations in circulating glucose or by the presence of non-oxidative advanced glycosylation end products (AGEs). The aim of this work has been to evaluate whether these variations generate changes in the expression of genes related to osteoblast differentiation and activity (OPG, RANKL, Runx2 and AGER) in primary cultures of human osteoblasts (hOB).
Material and methods: 12 patients were studied, belonging to three groups: 4 with osteoporotic fracture, 4 with osteoporotic fracture and DM type 2, and 4 patients with osteoarthritis, but who were not osteoporotic or diabetic (control group), with an average age of 80 ± 8, 84 ± 10 and 66 ± 11 years, respectively. Primary cultures of hOB from trabecular bone were carried out, to which were applied different stimuli over 24 hours. The gene study was carried out using real-time PCR.
Results: The genetic expression of RANKL was seen to increase in the diabetic group, although not to a significant degree, in the cultures which were high in glucose and high in glucose supplemented by AGEs (1.9 and 4.6 times higher vs control conditions; 2.3 and 4.4 times vs control group, respectively). The RANKL/OPG ratio stayed constant in the control group, however, in the diabetic group an increase was seen in all experimental conditions. In the case of Runx2 we found a significant increase in expression in the diabetic group with respect to the control group in the culture high in glucose and AGEs (OA = 1.08 ± 0.43; OP+DM = 3.33 ± 0.73; p = 0.039). No significant changes in the expression of OPG and AGER with respect to the control condition were observed for any of the culture conditions, in any of the patient groups.
Conclusions: The presence of a hyperglycaemic environment and AGEs alters the genetic expression of RANKL, of the RANKL/OPG ratio and Runx2 in osteoblast cultures from diabetic patients with hip fractures. These variations could generate changes in bone remodelling which could explain, at least partly, the lower bone resistance and the increase in the incidence of non-traumatic fractures in these patients.

Key words: *osteoporosis, fracture, diabetes mellitus, osteoblasts.*

Introduction

Osteoporotic fractures have a high prevalence in developed countries. Among these fractures, those of the hip are the most devastating due to their high mortality and the low number of patients who manage to recover a sufficient degree of functional activity to allow them to be independent. Diabetes mellitus (DM) is a metabolic disease which is also common in the population, with high mortality and morbidity, whose prevalence increases with age, as is the case with osteoporosis[1].

In patients with DM type 2 (DM2) it has been possible to confirm that, in spite of their having increased levels of bone mass, there is an incidence of osteoporotic fractures 2.8 times higher than in the general population, it being postulated that the disease itself, or the complications which originate from it, may alter skeletal bone remodelling, affecting bone formation and/or resorption, and with this, bone resistance[2]. Among those mechanisms which are considered to be implicated in this lower bone resistance are included: a deficit or resistance to insulin, the hyperglycaemia to which the bone and the microenvironment of the bone medulla are subject, the higher concentrations of the advanced glycation end products (AGEs) and their effects on the proteins of the bone matrix[3,4], the alteration in production of adipokines and cytokines and its negative effects in the bone cells and, finally, the damage that the neuromuscular system may exert on the skeleton, leading to a greater propensity to falls in these patients[5]. In spite of the fact that there are many factors postulated, there are few studies which analyse the importance of each of them, or the mechanism acting intimately on the deterioration of bone metabolism[6,7].

In the process of bone formation the signals which determine differentiation, replication and survival of the osteoblast cells will be critical for correct bone metabolism. Among these signals will be determinant genes included in the OPG/RANK/RANKL system, others such as Runx2, and maybe also those responsible for non-oxidising advanced glycation end product receptors (AGER). In DM the number and activity of bone-forming cells may be altered, as well as the response of these cells to local or systemic factors which contribute to bone remodelling[8].

OPG/RANK/RANKL is the main system of communication between osteoclast and osteoblast line cells, through which most systemic medicines, cytokines and growth factors which have an influence on bone remodelling work[9].

Runx2 is one of the multifunctional transcription factors which controls the development of the skeleton through the regulation of the differentiation of chondrocites and osteoblasts, directing the multipotential mesenchymal cells towards the osteoblast cell line[10] and triggering the expression of most of the genes which code for the proteins of the extracellular matrix. Runx2 $^{-/-}$ mice show a total lack of bone from birth[11].

The advanced glycation end product receptors (AGER) bond with a wide variety of structural and functionally related ligands, including the AGEs, such as pentosidine and carboxymethyl-lysine. The combination of AGEs –AGER promotes an overexpression of AGER, resulting in a permanent state of cellular activation, which it is thought contributes to the pathology of chronic disorders such as diabetes[12]. The AGEs form slowly with age in response to physiological levels of sugars, as well as being increased in hyperglycaemic environments, as is the case with diabetes, which is also associated with chronic inflammatory complications[13,14]. They combine with the membrane receptors (AGER) on the surface of the osteoblast line cells triggering intracellular signals which result in responses such as the expression of RANKL, the promotion of osteoblast differentiation and activation, and with this, bone resorption[15], as well as inducing osteoblast apoptosis[16].

The influence of hyperglycaemia or AGEs on the expression of genes related to bone metabolism has been studied before in animal models, in cell lines, and in primary cultures of osteoblasts from patients with arthrosis[17,18], but not with diabetic disease, as is the case with this study.

Given that to date there is very little knowledge about the influence of DM2 on bone metabolism and that it is not known how high levels of glucose and/AGEs may influence osteoforming cells and the expression of these genes (OPG, RANKL, Runx2 and AGER), we have proposed this study, which has as its main objective the analysis of these aspects in patients with DM2 and non-traumatic hip fracture.

Material and methods

Subjects of the study

We included 12 patients belonging to three study groups: 4 patients with non-traumatic hip fracture and DM2 (OP+DM group formed of 4 women), 4 patients with non-traumatic hip fracture without DM (OP group formed of 2 women and 2 men), and 4 patients subject to arthroplasty of the hip due to problems of osteoarthritis, without history of either osteoporosis or DM2, as a reference group (OA group formed of 3 women and 1 man).

The inclusion criteria for the OP+DM group was to have suffered from DM2 for a minimum of 5 years since diagnosis, as well as having a fragility fracture of the hip, due to a fall from a height lower than the height of the individual, without any acceleration mechanism. For the patients in group OP, to have had a hip fracture due to fragility without diabetic syndrome. And lastly, those in the OA reference group, not having previously been diagnosed with either diabetes or osteoporosis, nor having history of fragility fracture since the age of 50. The exclusion criteria for all the groups were the taking of medicines which have an influence on bone metabolism (corticoids, contraceptives, antiresorptives, immunosuppressors, glitazones) or having endocrine or systemic diseases with an influence on bone remodelling, as well as treatment for tumours in the last 10 years.

The sampling period was 6 months and all subjects came from the traumatology and orthopaedic service of the Virgin Macarena University Hospital in Seville. The patients were informed and gave their written consent, and the trial was approved by the ethics and health research committee of the hospital. In addition, the participants were subject to a questionnaire regarding their age, years of menopause in the women, toxic habits (alcohol and tobacco), semiquantitative consumption of calcium by means of a survey of daily intake of milk and milk-derived products (estimating each glass of milk or portion of cheese to be 200 mg of calcium), personal and family history of first degree fractures, chronic taking of medicines and concomitant diseases. For those patients in the OP+DM group, also included were the number of years the disease had been in development, hypoglycaemic treatments and presence/absence of chronic complications of the diabetic disease itself, such as retinopathy, nephropathy or arteriopathy. The height and weight of all patients was measured and their BMI calculated.

A blood sample was taken from all patients for the first 4 days after the episode of fracture, to determine the following blood biochemistry parameters: glucose, urea, creatinine, enzymes of hepatic function, total alkaline phosphatase (AP), calcium and phosphorus (Autoanalizer DAX-96), glycated haemoglobin (HbA1c) (HPLC); 250HD, PTH, insulin growth factor 1 (IGF-1), marker for bone resorption (β-Crosslaps) and formation (P1NP) (ELISA).

The biopsies of femoral bone were processed in sterile conditions immediately after being extracted by surgery, followed by the carrying out of cell cultures, as will be detailed in the following section.

Cell cultures

We carried out primary cultures of human osteoblasts (hOB) from explants of trabecular bone of 1-2 mm, extracts from the femoral heads biopsied. These were rinsed with PBS and subsequently distributed in 90 mm Petri dishes at a ratio of 10-15 explants per dish, attempting to obtain 3 to 5 dishes for each subject.

They were incubated in DMEM medium (4.5 mM of glucose), supplemented with 10% foetal bovine serum (FBS), 0.5% fungicide, 1% L-glutamine, 1% Na-Pyr and 1% of antibiotic (100U/ml of penicillin and 100 μg/ml of streptomycin) at 37ºC and 5% CO_2 for 7 days.

The culture medium was changed twice a week until subconfluence was reached. Once this moment had arrived (after between 4 to 6 weeks) we carried out a cell passage. We trypsinised (Trypsin-EDTA) and plated the cells (300,000 cells/well on dishes of 6 wells) in the same medium as already mentioned.

On reaching sub-confluence again, the cells were washed with saline PBS buffer and incubated for 24 hours with the same medium, without FBS to have the cultures at the same stage of growth at the start of the experiment. Different conditions of culture were established over 24 hours to evaluate the effect of high concentrations of glucose and AGEs on the functioning of the osteoblasts: a) medium low in glucose (4.5 mM), b) rich in glucose (25 mM), c) rich in glucose (25mM) supplemented with AGEs (0.1 mg/ml) (Advanced Glycation Endproduct-BSA. Calbiochem. USA and d) medium low in glucose supplemented with manitol (25 mM) to discount the possible effect of the hyperosmolarity which a high concentration of glucose could exert on osteoblasts in culture.

The following were analyzed in all cultures:

1. Cell viability, calculated with the TripanBlue exclusion test at 0.5%.

2. Bone alkaline phosphatase (BAP) activity, measured after incubation for 1 hour at 37ºC in 0.1 M of NaHCO3- Na2CO3 pH 10, 0,1% Triton X-100,2 mM MgSO4 and 6 mM PNPP. The reaction was stopped with 1M of NaOH and the absorption measured at 405 nm. The percentage of changes in the BAP activity in relation to the value found in the control was calculated using the formula: M= absorbance value at 405 nm/absorbance value at 560 nm. The percentage change= (M of the control M-test)/M of the control x 100.

Quantification of the expression of mRNA (OPG, RANKL, Runx2 and AGER)

Using the cells gathered from each of the experimental culture conditions an extraction of total RNA was carried out (High Pure RNA Isolation. Roche, USA). The concentration of RNA was measured at 260 nm (GeneQuant, Amersham Biosciencies). Subsequently, the RNA obtained was retrotranscribed to cDNA (QuantiTec Reverse Transcription, Qiagen).

The analysis of the gene expression of the different genes of the study was carried out using PCR real time (QuantiTec SYBR Green PCR, Quiagen; Primers Applied Biosystem).

The results for each of the genes studied were referenced to those obtained for ribosomal gene 18S and in turn, with the control condition (4.5 mM glucose).

Statistical analysis of the results

For the statistical analysis of the results we used SPSS version 18.0. The individual results were reviewed to avoid the loss of data and unusual values. All the experiments were reproduced in duplicate and the descriptive statistical data of the numerical variables were expressed as mean ± standard deviation. First, the homogeneity of variance of the variables was analysed. In those cases in which homoscedasticity was confirmed an ANOVA test was applied with Tukey's HSD post-hoc analysis. For those which showed heteroscedasticity, a Welch F test was applied with a Games-Howell post-hoc analysis. Correlation studies were made using the Pearson or Spearman correlation test depending on the normal distribution, or not, of the variables. In all cases a significance level of $p<0.05$ was required.

Results

The results we present here are preliminary, taking into account the fact that only 4 subjects per study group were evaluated. The characteristics of the patients in the three groups studied, as well as the average values of the blood parameters analysed are found in Table 1.

The age of the patients in the OA group was significantly lower than the age of the other groups, which means that for the statistical comparison of the other parameters an adjustment for age was made. The BMI was lower, although not statistically different, in the OP group. The renal function was normal and comparable across the three groups. The levels of glucose when fasting and HbA1c were in the normal range, without showing significant differences between the three groups, while the OP+DM patients were those who had the highest value, with HbA1c reaching levels 25% higher in this group, with respect to the other groups studied. In terms of the parameters related to calcium metabolism, only the levels of phosphorus and AP were significantly different when comparing the three groups, the levels of phosphorus being lower, and those of AP higher, in the OP group in relation to the OA and OP+DM groups. The rest of the parameters, while not showing significant differences, had some noteworthy aspects. The levels of vitamin D were, in all cases, below 20 ng/ml and somewhat lower in those patients who had had a hip fracture, with or without DM, with respect to the controls (average values of 9.6 ng/ml and 9.2 ng/ml vs 12.3 ng/ml, respectively). The levels of PTH were higher in the OP group, as well as the markers for bone remodelling, both for formation and resorption, P1NP and β–CrossLaps.

The blood levels of IGF-1 were lower in the two groups with hip fracture (average values in OP = 25 ng/ml, in OP+DM = 37.7 ng/ml and in OA = 41.8 ng/ml), becoming significantly different in the OP group compared with the OA group (p= 0.011).

Cell viability and BAP

No significant differences were found in any of the groups for any of the conditions studied, with all the cultures having a viability higher than 85% and BAP staining higher than 95%.

RT-q-PCR

In the study of the expression of the osteogenic genes studied we found high levels of interpersonal variation.

The results of the expression of OPG are represented in Figure 1. None of the different culture conditions significantly influenced the gene expression of OPG in the three groups studied, nor was any difference seen between the three groups. Only the situation of hyperglycaemia and even more, the combination of hyperglycaemia and AGEs, had a higher expression of OPG in the OP group, reaching a level 1.7 times that of the control group.

The gene expression of RANKL (Figure 2) was seen to increase in the OP+DM group, although not significantly, with the expression higher in the condition high in glucose, both in respect of the control condition and the control group (1.9 and 2.3 times higher, respectively). The same occurs in the condition high in glucose supplemented with AGEs (4.6 times vs control condition and 4.4 times control group, respectively). The results show a decrease in the gene expression of RANKL in the presence of a high concentration of glucose, both in the control and in the OP group. However, in the presence of the AGEs, the expression was similar to the control condition in both groups.

The values of the RANKL/OPG ratio (Figure3) remain constant in the control group. However, in the OP+DM group they are seen to be increased in all of the experimental conditions. With regard to the OP group a reduction occurs in the presence of high glucose, and an increase, similar to that we observed in the diabetic group, with high glucose plus AGEs.

In the case of the gene expression of Runx2 (Figure 4) we found a significant increase in the OP+DM group with respect to the control group in the experimental condition which combined high glucose and AGEs (OA = 1.08 ± 0.43; OP+DM = 3.33 ± 0.73; p=0.039). In this same condition we also observed an increase in the expression in the OP group, although it was not significant.

Lastly, the results of the gene expression of AGER (Figure 5) were very similar between the groups studied, being higher than in the control condition. However, these results were not significant in any of the groups and for none of the experimental conditions.

We didn't find any statistically significant correlation between the biochemical and anthropometric parameters (Table 1) and those genes involved in bone metabolism which were studied (Figures 1-5).

Discussion

The most significant results of this study show us that the addition of glucose, at high concentrations, and above all the combination of glucose and AGEs, to cultures of hOB from patients with DM2 and hip fracture increases the expression of the RANKL genes, the RANKL/OPG and Runx2 ratio, compared with a person with neither hip fracture or DM.

In agreement with our results, Li et al. demonstrated in studies in rats that high levels of glucose in the culture medium induce higher osteoblast differentiation in ligament cells stimulated to become osteoblasts, through a significant increase in levels of gene expression for Runx2[19]. However, other authors have described other different results depending on the type of cells used, the levels of glucose in the culture medium and the time exposed to it, these factors not being consistent[20-23].

It has been possible to show that transgenic mice which overexpress Runx2 also have an incre-

Table 1. Anthropometric characteristics and blood biochemistry parameters of the groups studied

	OA (n=4)	OP (n=4)	OP+DM (n=4)	
Age (years)	66 ± 11 *	80 ± 8	84 ± 10	*p=0.04
BMI (kg/m²)	30.8 ± 2.8	23.6 ± 2.3	31.5 ± 4.9	
Creatinine (mg/ml)	0.8 ± 0.05	0.9 ± 0.05	0.8 ± 0.06	
Glucose (mg/dl)	84.8 ± 4.9	97.5 ± 0.5	100.7 ± 12.9	
HbA1c (%)	5.1 ± 0.3	5.1 ± 0.5	6.5 ± 0.6	
25(OH)D (ng/ml)	12.3 ± 3.1	9.2 ± 3.2	9.6 ± 0.7	
PTH (pg/ml)	48.1 ± 10.6	72 ± 55	35 ± 4.9	
PIPN (ng/ml)	38.01 ± 16.2	42.5 ± 1.2	67 ± 20.3	
β-CrossLaps (ng/ml)	0.45 ± 0.09	0.83 ± 0.07	0.62 ± 0.19	
Phosphorus (mg/dl)	3.3 ± 0.1	2 ± 0.3 *	2.5 ± 0.3#	*p=0.004 #p=0.022
AP (U/L)	160.3 ± 16.3	247.5 ± 25.5 *	181 ± 39.4	*p=0.04
Ca corrected (mg/dl)	9.6 ± 0.2	9 ± 0.1	9.5 ± 0.3	
IGF-1 (ng/ml)	41.8 ± 2.9	25 ± 0.01 *	37.7 ± 12.7	*p=0.011

*OA vs OP; # OP vs OP+DM

ase in the expression of RANKL, giving as a result mice with a significant loss of bone mass. In this case the authors associate these findings with the blocking of osteoblast differentiation, which is to say, that the overexpression of Runx2 is related to a greater number of less differentiated osteoblasts which express a greater quantity of RANKL, activating osteoclastogenesis and thus generating a greater number of mature osteoclasts[24]. The presence of high blood concentrations of glucose and AGEs are normally very frequent metabolic changes in diabetic patients, as is apparent from our results, causing an overexpression of Runx2 in osteoblast cells, as well in as the expression of the RANKL/OPG ratio, which may result in an increased rate of remodelling and have a negative impact on bone resistance.

We found in our study an increase in RANKL and the RANKL/OPG ratio, highest above all in the OP+DM group. De Amorim et al. found that in diabetic rats with tibial fracture there is an increase in the RANKL/OPG ratio with respect to healthy rats, which supports our results[25].

What we find interesting is that the osteoblasts from patients with hip fracture, with or without DM2, are those which have a higher variability in the expression of the genes in the study resulting from the stimulus taking place in the different situations of the *in vitro* cultures. Thus, in earlier research carried out by our group in cultures of hOB from patients with hip fracture as against patients with arthrosis, we also confirmed that those patients with osteoporosis were those who had the greatest modifications in gene expression under the different stimuli[26-28]. This may indicate that, *in vivo*, these cells of osteoporotic patients are already conditioned by the environment in which they are found, to response levels higher than in an individual with healthy bone metabolism. Equally, those patients with DM2 with altered bone metabolism induced by hyperglycaemia and habitual oxidative stress, are also those who respond more in the *in vitro* conditions with which we have experimented.

The gene expression of AGER is seen both in the high glucose condition and in glucose supplemented with AGEs in the control (OA) and osteoporotic (OP) groups, but not in the diabetic group (OP+DM), which are similar to the baseline condition. These results coincide with those obtained in MC3T3E1 cells by Mercer et al.[17] and in human osteoblasts by Franke et al.[18], where they analysed the expression of AGER in cultures exposed to AGEs. In this case, it is suggested that as a consequence of the presence of a higher concentration of AGEs a greater activation of AGE-AGER is produced, which would cause osteoblast dysfunction. The results, with regard to the expression of AGER, in the OP+DM group indicate that the osteoblasts in these patients may have suffered some kind of habituation to high extracellular levels of glucose and AGEs, which makes them not react to

Figures 1-5. Effect of a high concentration of glucose and glycation end products on the expression of genes related to bone metabolism in primary cultures of human osteoblasts. The primary cultures of hOB were incubated until confluence, after which a cell passage was carried out. Once confluence was reached again the culture conditions were differentiated for 24 hours: normoglycemic (4.5 mM of glucose), osmotic control (25 mM of manitol), high glucose treatment (25 mM of glucose) and high glucose treatment supplemented with AGEs (25 mM of glucose and 0.1 mg/ml of AGEs). An analysis was carried out of gene expression in response to the treatments using quantitative real time PCR. The ΔΔCt method was used and the results were referenced both to the endogenous 18S Ribosomal gene, as well as to the control condition (4.5 mM of glucose, which was established as 1.

Figure 1. OPG gene expression

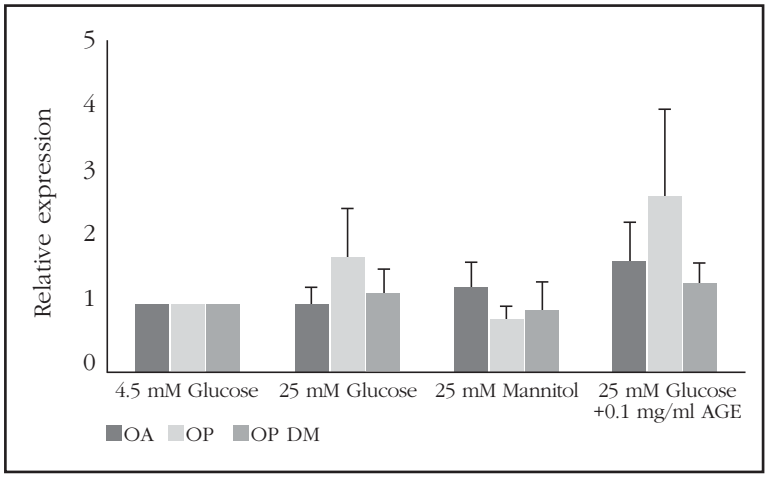
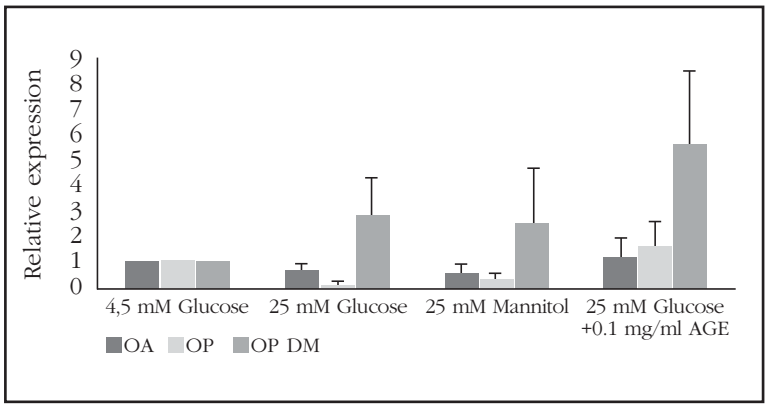


Figure 2. RANKL gene expression



these stimuli, at least during the first 24 hours of treatment. The interaction of AGEs with their receptors changes cell signalling, promotes an increase in the generation of reactive oxygen species (ROS), with the consequent oxidative stress. In turn, the long term hyperglycaemic environment, such as occurs in diabetes, increases the production of AGEs and of ROS, which may cause a decrease in the proliferation, and an increase in the apoptosis, of osteoblasts[29].

We have been able to confirm that those patients with hip fracture without DM have high levels of PTH and low levels of IGF-1, both conditions being associated with senile osteoporosis and hip fracture. It is known that with age there are lower levels of vitamin D, as a consequence of a lower provision, lower absorption and less exposure to sun, which results in secondary hyperparathyroidism, with the consequent increase in remodelled bone and a higher risk of suffering fractures[30]. In people of an advanced age low levels of blood IGF-1 are also described which is correlated with low levels of bone mineral density and with an increased risk of fracture[31].

While it is true that most of the results we found may not have been statistically different due to the small sample size, we also have to take into account that the group of patients with DM2 had been developing the disease over a short period (average 5 years) and with highly adequate metabolic control (HBA1c average of 6.5%). As is known, the complications of diabetes are more acute both the longer its period of development and the more altered its carbohydrate metabolism is[3]. Among the limitations of this study the most significant is the fact that it was not possible to count on a group of truly healthy people from who we could obtain bone biopsies, having to use as reference people with arthrosis, who in general and given the nature of this pathology, are always going to be younger than patients with hip fracture, bearing in mind that age is one of the independent factors with most influence on changes in bone remodelling. Finally, it would be a good idea to analyse whether or not the alterations found in genes have repercussions at the level of proteins.

In conclusion, and in view of our results, we are able to say that the presence of hyperglycaemia and AGEs alter the gene expression for RANKL, the RANKL/OPG ratio and Runx2 in osteoblast cultures from patients with osteoporotic fracture and in diabetics with this type of fracture, especially in the latter. This may generate alterations in bone remodelling (higher levels of β-Crosslaps and PINP) which may explain, at least in part, the lower bone resistance and the increase in the incidence of non-traumatic fracture in these patients.

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Figure 3. Ratio RANKL/OPG

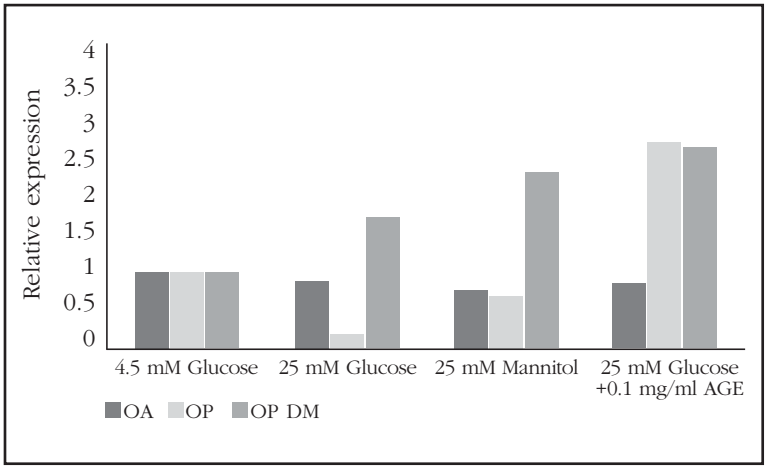


Figure 4. Runx2 gene expression

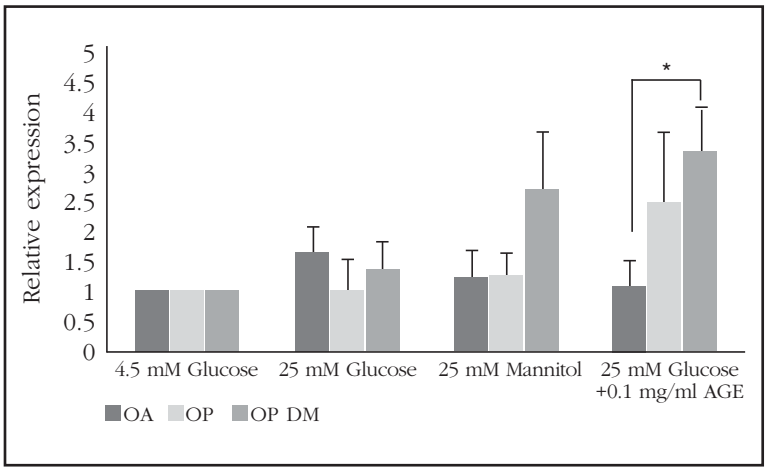
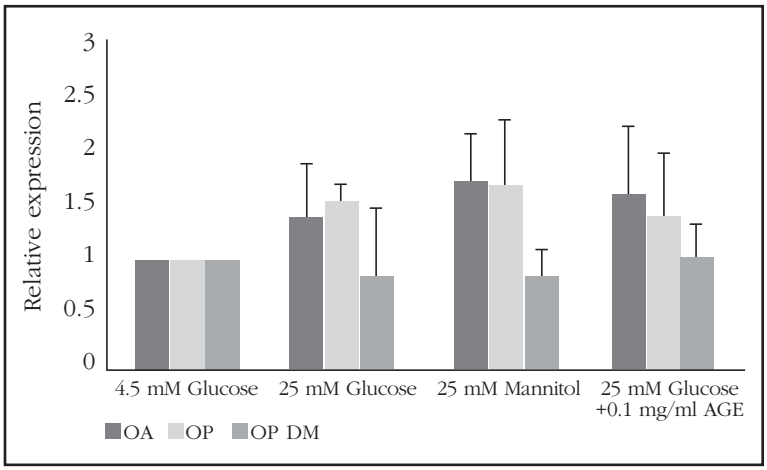


Figure 5. AGER gene expression



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Cobb angle, vertebral deformity and fractures in alcoholic patients

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Summary

Background: Hypercyphosis and vertebral deformity are related to vertebral fractures. There are no studies in chronic alcoholics.

Objective: To analyse the relationship which exists between the Cobb angle and different degrees of vertebral deformity, and bone mass and various variables related to bone metabolism in chronic alcoholic patients.

Material and methods: 57 alcoholic males aged 52 ± 12 years were included. The Cobb angle was calculated and the degree of vertebral deformity of T7, T8, T9 and T10 was measured using MorphoXpress® and thoracic X-ray. The bone mass in the spine and hip were determined using a DXA Hologic Walthan 2000, and exiting clinical fractures with the clinical history. In addition, the nutritional state, the degree of alcoholism, variables of hepatic function, the presence of hepatic cirrhosis, and bone metabolism, were analysed. The results were also studied in 20 controls of similar age and of the same sex.

Results: The patients had a greater Cobb angle in comparison with the controls (30 ± 9º vs 17 ± 5º, respectively, $p<0.001$). Those with cirrhosis had lower bone mass than those without in the lumbar vertebrae ($p<0.01$) and femoral neck ($p=0.02$). The deformities in T7, T8, T9 and T10 were associated with a greater cyphosis, longer period of consumption and with existing vertebral fractures ($p<0.01$), non-vertebral fractures ($p<0.002$) and hip fractures ($p<0.001$). There were 65 existing fractures, 46 in the rib, 12 vertebral and 7 in the hip. The patients with a higher Cobb angle had more vertebral ($p<0.01$) and non-vertebral ($p=0.04$) fractures, as well as a longer period of alcohol consumption ($p=0.02$).

Conclusions: Chronic alcoholics have greater cyphosis than the controls. Wedge or biconcave vertebral deformities are related with a greater cyphosis, higher consumption of alcohol and existing fractures. In this series a higher Cobb angle is related to existing vertebral fractures. The most intensive drinkers had a higher Cobb angle and more fractures.

Key words: *hypercyphosis, Cobb angle, vertebral fractures, alcoholism.*

Introduction

The chronic alcoholic patient, in the fourth or fifth decade of their life, has a reduced bone mineral density (BMD) comparable with an old person[1]. This decrease in BMD, combined with an irregular lifestyle, with a propensity to traumatisms due to accidental falls or to aggressive attacks led Oppenheim (1977)[2] to coin the term "battered alcoholic syndrome" to designate those alcoholic patients with three or more fractures in different stages of development.

The bone pathology of the chronic alcoholic consists essentially in osteoporosis of low turnover[3] in which malnutrition, chronic hepatopathy, changes in the pancreas and hormonal changes, and life style (unemployment, marginalisation, little exercise) play an essential role.

In men, the frequency of an osteoporotic vertebral compression fracture is estimated at approximately 5%, which results in a loss of vertebral height and/or angulation, with the progressive development of thoracic kyphosis[4].

In chronic alcoholics, the relationship between bone mass and fractures has been little studied. The prevalence of fractures diagnosed though thoracic radiography in alcoholics has varied in different series analysed from 8.7 to 36%[5]. Earlier studies have described in alcoholic patients an association between vertebral fractures and peripheral fractures in spite of a BMD above the fracture threshold, suggesting the use of conventional X-ray imaging techniques combined with bone densitometry for the diagnosis of osteoporosis in these patients[6].

The changes in curvature of the thoracic kyphosis may be related to the intensity and type of vertebral or non-vertebral deformity or fracture which exist in alcoholic patients. Therefore, the objectives of this study were to compare the Cobb angle of alcoholic patients with those of a control population and to analyse the relationship which exists between this angle and the vertebral deformity measured with the use of a MorphoXpress®, with the BMD, variables of bone metabolism, hepatic function, degree of alcoholism and previous vertebral and non-vertebral fractures.

Material and method

We designed a prospective unicentric study in which we included 57 male alcoholic patients admitted to the internal medicine service of the University Hospital of the Canary Islands between May 2005 and June 2007 consecutively, due to alcoholism-related organic complications, alcoholic abstention syndrome or decompensation of hepatic cirrhosis. We classified the patients into cirrhotic or non-cirrhotic as a function of clinical, analytical and imaging variables.

Excluded from the study were those patients with neoplastic diseases, chronic hepatopathies of a different origin, or those with HIV infection, in order to avoid confusion at the time of the study, as well as those who were taking drugs which may interfere with calcium metabolism. The control group was composed of 20 healthy males who drank less than 10g/ day of alcohol.

Once the informed consent had been given, the clinical history was reviewed and the history and locations of earlier fractures, degree of the alcoholism, organic and clinical repercussions of the alcoholic disease, hepatic cirrhosis (ascites and encephalopathy) and nutritional state were obtained.

- In addition, general and routine analyses were carried out to determine the following:

1- Hormones related to bone metabolism: IGF-1, thyroid hormones (free T4), parathormone (PTH), vitamin D, cortisol, estradiol, testosterone.

2- Variables related to bone turnover: osteocalcin, telopeptide, osteoprotegerin (OPG) and RANKL.

3- Hepatic function evaluated through prothrombin activity, albumin and blood bilirubin.

- An analysis of the nutritional status of the patients was made by calculating the subjective global nutritional assessment (SGNA)[7] where:

1- Well nourished: 0-2 points

2- Moderate malnutrition: 3-4 points

3- Severe malnutrition: 5-10 points

For this assessment an anthropometric evaluation was carried out using dynamometry, tricipital cutaneous fold, and brachial perimeter.

- Posterior-anterior and lateral X-rays of the thorax: with the lateral thoracic X-ray the degree of thoracic curvature was determined by calculating the Cobb angle between T1 and T12, and the morphology of the vertebral bodies were studied for the diagnosis of existing vertebral fractures. Existing vertebral fractures were defined at the time of inclusion in the study as a reduction of - at least - 20% in the anterior medial or posterior height of the vertebral body, according to the Genant criteria, or the presence of visible vertebral wedging or crushing.

- MorphoXpress®[8] (deformity and fracture): the vertebral morphometry was evaluated in T7, T8, T9 and T10. Both evaluations were carried out by a single observer. The MorphoXpress®[8] system is a digitised method of reading of standard or digital X-rays of the dorso-lumbar spinal column in their lateral projection. After the digitisation of the X-ray image it is compared by a system expert with a database internal to the system which contains more than 3,000 images, with the aim of identifying tridimensionally the different vertebrae analysed. After this tridimensional study, the equipment positions six points in each vertebra analysed, allowing the operator to modify these points to adjust them for a better view. In evaluating the image thus obtained, the software calculates the different vertebral heights from the positioned points, and detects the existence and severity of vertebral deformity and fracture. This method has shown a high level of precision and little inter-observer variability[8].

- Densitometry: we determined the bone mass in the spinal column (L2, L3, L2-L4), femoral neck of the hip, the extremities, rib cage, dorso-lumbar spine and pelvis, using DEXA with HOLOGIC® QDR-2000 (Waltham, MA, USA).

This study was approved by the ethics committee of our centre (2009/23) and complies with the 1975 Helsinki Declaration.

Table 1. General characteristics of patients and controls

	Patients (n=57)	Controls (n=20)	p
Age	52 ± 12	50 ± 9	NS
Body Mass Index (kg/m^2)	24.1 ± 3.1	25.6 ± 2.8	NS
Subjective nutritional assessment (normal/moderate/severe)	30/12/15	20/0/0	p<0.001
Consumption of alcohol (g)	201 ± 79	<10	
Cobb angle (degrees)	30 ± 9	17 ± 5	p<0.001
Osteocalcin (ng/ml)	3.3 ± 3.1	7.0 ± 2.5	p<0.001
Telopeptide (ng/ml)	0.59 ± 0.40	0.19 ± 0.10	p<0.001
Vitamin D (pg/ml)	29.1 ± 15.2	82.5 ± 27.6	p<0.001
IGF-1 (ng/ml)	95.9 ± 101.1	179.32 ± 97.25	p<0.001
Serum PTH (pg/ml)	77.2 ± 136.4	75.2 ± 105.8	NS

NS: not significant

Statistical analysis

Firstly, it was determined if the variables had a normal distribution using the Kolmogorov-Smirnov test. Even though they mostly showed a parametric distribution, in some, such as fracture, IGF-1, PTH, osteocalcin and RANK, it was non-parametric. Therefore, for the univariate inferential statistics, in the case of parametric variables the Student-t test was used to compare a variable between two groups, the VARIANZA analysis (in the case of three or more groups) and, subsequently, the Student-Newman-Keuls (SNK) test to discern between which groups differences were established, and the Pearson correlation test to analyse the relationships between two quantitative parameters. Given the relationship with bone mass to age, a covariant study was conducted with these parameters.

In the case of non-parametric distributions, the Mann-Whitney U test to analyse differences between 2 groups, and Kruskall-Wallis to analyse differences between 3 or more groups, as well as Spearman's correlation, were used.

Results

The 57 alcoholic patients studied had an average age of 52 ± 12 years and were all drinkers up until the time of admission, with a consumption of more than 201 ± 79 g/day of alcohol. The average period of consumption was 28 ± 11 years. The total accumulated dose of alcohol was 29 kg –alcohol/kg (Table 1).

53% of the patients were cirrhotic (29 patients) and 47% non-cirrhotic (28 patients). There were no differences between the ages of the two groups (p=0.27).

The average Cobb angle between T1 and T2 in the group of patients was 30 ± 9º and in the controls, 17 ± 5º (p<0.0001) .

The deformities of the vertebrae studied are expressed as a percentage of the loss of height in the anterior wall (wedging), central height (biconcave) and global (crushing).

The averages of wedging in T7 were 16 ± 9%, of biconcave deformity 15 ± 7% and of crushing 3 ± 4%.

The wedging of T8 was an average of 13 ± 8%, while the biconcave deformity and crushing were 13 ± 9% and 10 ± 8% respectively. The vertebral wedging of T9 was an average of 14 ± 9%, the biconcave deformity 15 ± 8% and the crushing 7 ± 6%. The wedge deformity in T10 was an average of 14 ± 9%, biconcave 15 ± 9% and crushing 2 ± 5%.

In the group of patients a total of 65 fractures were detected: 46 costal fractures, 12 vertebral fractures and 7 fractures of the hip. The number of fractures was similar in the cirrhotic and non-cirrhotic patients (vertebral, non-vertebral and costal).

66% of the patient were smokers with a packets/year index (PYI) averaging 29 ± 22. There were no differences in the Cobb angle (p=0.6) or in vertebral morphometry (p=0.2) between smokers and non-smokers.

The cirrhotic patients had less bone mass than the non-cirrhotic in the different areas analysed (Table 2). The Cobb angle in cirrhotic patients (29 ± 9º) and non-cirrhotic (28 ± 8º) was similar (p=0.6). The intensity of the thoracic kyphosis was not related to the Child-Pugh stage, nor to other clinical variables (ascitis and encephalopathy) or analyses of liver function (prothrombin, albumin and bilirubin). In the group of patients the wedging of T7 (p<0.01) and the biconcave deformity of T8 were related to a greater Cobb angle.

Table 2. Bone mineral density in cirrhotic and non-cirrhotic

	Cirrhotic (n=29)	Non-cirrhotic (n=28)	P
Dorsal column	0.9 ± 0.1	0.9 ± 0.1	NS
Lumbar spine	0.9 ± 0.2	1.0 ± 0.2	p=0.01
Femoral neck	0.8 ± 0.1	0.9 ± 0.2	p=0.02
Total hip	0.8 ± 0.1	0.9 ± 0.1	p=0.05
Pelvis	0.9 ± 0.1	1.1 ± 0.1	p=0.008
Right leg	1.1 ± 0.1	1.2 ± 0.2	p=0.01
Left leg	1.2 ± 0.1	1.2 ± 0.1	NS
Right arm	0.7 ± 0.1	0.8 ± 0.1	p=0.001
Left arm	0.7 ± 0.1	0.8 ± 0.1	p=0.001
Right rib cage	0.5 ± 0.1	0.6 ± 0.1	p=0.02
Left rib cage	0.5 ± 0.1	0.5 ± 0.1	p=0.001

In terms of the deformities, we found that the crushing of T7 was related to the presence of ascitis (p=0.009) and high values of PTH (p=0.02) and free T4 (p=0.01), while the wedging was related to a smaller tricipital skin fold (p=0.04). The wedging of T8 was related to a reduction in prothrombin activity (p=0.01) and the biconcave deformity with a reduction of osteocalcin (p=0.03). The wedging of T9 was related to the presence of ascitis (p=0.04), low values of IGF -1 (p=0.01) and raised levels of cortisol (p=0.005) while the biconcave deformity of T10 was related to free T4 (p=0.01).

In terms of the patients' existing vertebral fractures, the fractured patients had a greater degree of kyphosis and, therefore, a greater Cobb angle in comparison with those who were not fractured (p<0.01) (Figure 1).

Those patients with vertebral fracture had a greater biconcave deformity of T7 (p=0.002) and T8 (p<0.01), as well as wedging of T8 (p=0.04). However, by introducing the amount of daily intake in grams and the period of consumption as covariables, we see that, with respect to the biconcave deformity of T7, the relationship is dependent on the period of consumption. This is not the case with T8. An existing fracture of any type was related to the biconcave deformity of T7 (p=0.02) and T10 (p=0.009), while in both cases this relationship depended on the period of consumption. The wedging of T10 was related to fracture of the hip (p<0.0001) and to costal fracture (p<0.002), although in this case the quantity of daily alcohol intake replaces vertebral deformity.

We found no relationship between the Cobb angle and hip or costal fractures.

Patients with a longer period of consumption had a higher Cobb angle (p=0.002) (Figure2) and greater T7 wedging (p=0.03) and T8 biconcavity (p=0.03).

Those patients with a fracture had a longer period of consumption in comparison with those with no fracture (p=0.04),and the intake was heavier, with a higher total accumulated dose (p=0.02).

Those patients with costal fractures consumed more alcohol daily (228 ± 96 g/day, p=0.03) in comparison with those with no fractures (163 ± 64 g/day, p=0.012) (Figure 3).

In this series we found no relationship between the Cobb angle and the variables relating to nutritional state, parameters and hormones of the calcium-phosphorus metabolism, or with the markers for bone synthesis or resorption.

Discussion

In alcoholic patients a decrease in bone mass is common, the effect being more intense in those with cirrhosis. Our patients had less bone mass in the lumbar spine, pelvis, extremities and hip; data in accord with earlier studies[9-11]. Osteopathy in the alcoholic is multifactorial. The alcohol exerts a double lesive effect on the bone; on the one hand, it affects bone synthesis due to osteoblast toxicity[12], while on the other, it increases bone resorption by stimulating osteoclast activity and osteoclastogenesis through IL-6 and the induction of RANKL[13]. In addition, its toxic effects on muscle and the nervous system appear to be related to a higher risk of falls. Finally, other factors related to a propensity to traumatism, falls, social marginalisation, and irregular meals, among others, contribute to bone loss and fractures in alcoholics[14-15].

The angle of thoracic kyphosis increases with age and is related with underlying osteoporosis and/or the presence of vertebral fractures[16]. Hyperkyphotic posture and postural changes offer the capacity for clinical prediction which the markers for osteoporosis do not[16]. Epidemiological studies have shown that hyperkyphotic posture is associated with a deterioration in pulmonary function, physical state, falls, fractures and mortality.

It is known that one of the effects of the consumption of alcohol on the metabolism is a 2.4-fold increase in the relative risk of vertebral fracture[17]. This study also underlines the importance of tobacco in vertebral fracture, observing that the concomitance of both factors in the same patient multiplied the risk of vertebral fracture. In our study the alcoholics had a greater Cobb angle in comparison with the controls, but smoking did not significantly increase it. In classifying the patients as cirrhotic or non-cirrhotic we found no differences, and the angle of kyphosis was not related to the degree of the underlying hepatopathy, nor with the nutritional state. However, the presence of ascitis was related with various degrees of deformities of the dorsal vertebrae. As is it logical to expect, those patients with greater vertebral deformity and with vertebral fractures had a higher Cobb angle, and, therefore, greater kyphosis. The different types of deformities in the vertebrae analysed were significantly related to existing vertebral, non-vertebral, and hip fractures. However, greater kyphosis was not associated with either non-vertebral or hip fractures.

The Cobb angle was not related to bone mass determined in the dorso-lumbar spine, pelvis, hip, rib cage or limbs, or with non-vertebral or hip fractures.

From a biomechanical point of view the square of the BMD is proportional to the resistance to compression of the trabecular bone, which means that small reductions in BMD would be associated with significant decrements in bone resistance[18]. *In vivo*, a high BMD does not necessarily imply a greater biomechanical resistance, which indicates that other factors independent of BMD are related to bone resistance.

These results concur with those of a study carried out with 76 chronic alcoholics with 27 vertebral fractures[6], in which no significant differences were found in the BMD in the lumbar spine in patients with or without vertebral fractures, although those patients with vertebral fractures actually had more peripheral fractures.

The intensity of the alcoholism is a factor related to the osteopathy of these patients[19]. In our study we included patients with significant alcohol intake, higher than 200 g of alcohol a day for more than 20 years, and we have observed a significant relationship between the quantity of consumption and vertebral deformity and an increase in the Cobb angle, there is also a relationship between the period of consumption and the angle of kyphosis (dose- and time-dependent). Hence, in the heaviest drinkers we find more episodes of fracture.

Figure 1. Cobb angle and vertebral fracture

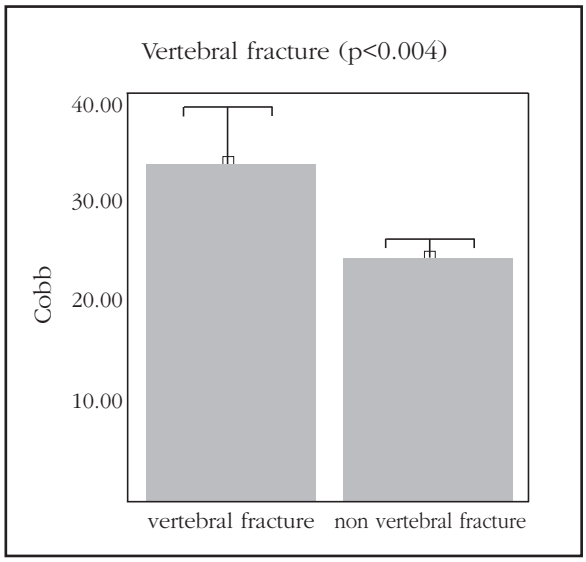


Figure 2: Cobb angle and time consuming

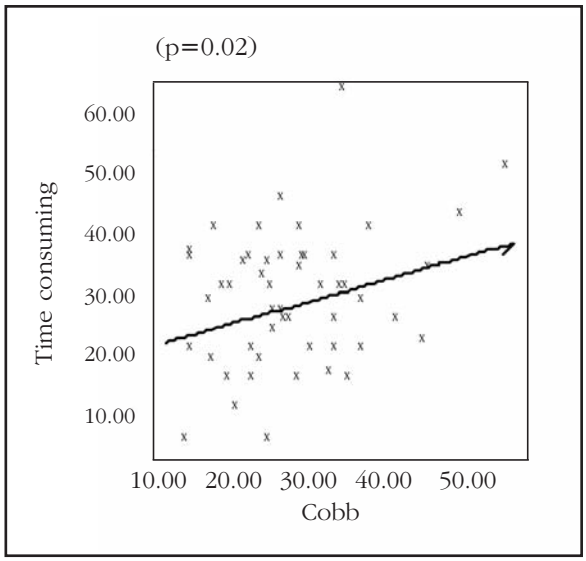
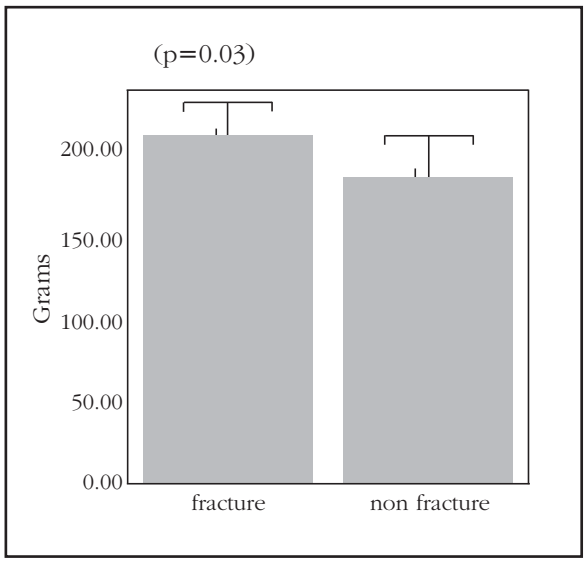


Figure 3: Rib fractures and daily alcohol consumption (grams)



The direct effect of alcohol on the osteoblasts is already an old observation. There are studies which describe a dose-dependent effect with an anti-proliferative action on the osteoblasts[20].

The quantity of bone mineral present in the skeleton depends on the quantity acquired during the skeleton's development and maturation phases, and which reaches its maximum value (peak bone mass) in adulthood. Genetic, nutritional, environmental and hormonal factors contribute negatively to the achievement of an adequate reserve of bone[18]. One of the greatest risks of developing osteoporosis is the attainment of a lower peak bone mass in youth[21]. The consumption of alcohol, common in adolescents and young people, tends to occur at this stage, which compromises the attainment of an adequate peak bone mass. Many of our patients started to drink at an early age and have continued, which results in structural and functional changes in the bone in the medium and long term[22]. The consumption of alcohol can affect different parts of the skeleton in different ways, and the vertebrae appear to be the most sensitive to damage after chronic consumption, and their recuperation after abstinence slower, which would result in skeletal changes which may persist, increase fragility and cause osteoporosis, deformity and fracture[22].

The use of MorphoXpress® allows the early diagnosis of deformity and vertebral fracture through the use of conventional X-rays, reducing the time needed for morphometry, increasing the accuracy of the process, with little intra- and inter-observer variability, and facilitating a sensitive following of its development vertebra by vertebra.

In this disease there is a high incidence of complications during the treatment of fractures[23]. Studies in rats suggest that alcohol exerts direct, dose-dependent biological effects on the process of consolidation of the fracture[20], essentially an anti-proliferative effect, and an inhibition of osteoblast function. Experimentally, in alcoholic rats subject to femoral osteotomy, a total absence of bone callusing compared with the controls in which the consolidation was complete, has been confirmed[20]. Chakkalakal et al.[20] described a defective bone repair, poor rigidity and demineralised bone matrix, with deficient mechanical properties, effects which improve with abstinence. Other studies found that ethanol inhibits rapid "intramembranous" bone formation which characterises normal consolidation in fractures, and promotes fibrosis instead of osteogenesis at the point of repair, by which the osteoid and fibrous tissue ossify, resulting in dysmorphic mineralisation, originating new tissue with poor biomechanical properties independently of the bone mineral content[24-25]. The essential differences are in the rigidity of curvature, strength and ash density of the tissue which forms the bone callus. Thus, these data reinforce even more the lesive effect which alcohol exerts on the skeleton. What is notable in this series is the absence of a relationship between vertebral deformity and fractures and markers for bone and for mineral metabolism. It is possible this is related to the irregular lifestyle of these patients with a propensity to falls and traumatisms which change bone morphology and increase the risk of fractures.

Conclusions

Chronic alcoholics show a decrease in BMD and a greater degree of kyphosis compared with the controls. Vertebral deformity - wedge or biconcave - are related with a greater kyphosis, higher consumption of alcohol and the presence of existing fractures. A greater Cobb angle is related with a higher prevalence of vertebral fractures in our patients, independently of BMD, hepatic function, nutritional state and bone metabolism. The most intensive drinkers had a greater Cobb angle and more existing fractures.

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Could the FRAX® index modify the treatment of osteoporosis?

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Summary

Introduction: The FRAX® index is an algorithm devised by the WHO which, by evaluating risk factors, calculates the absolute risk of suffering any osteoporotic fracture or hip fracture in the subsequent 10 years. The aim of this work is to ascertain the risk of fracture in patients with suspected osteoporosis, using the FRAX® tool, and to ascertain how therapeutic decisions would be modified if these criteria were used.

Patients and method: The patients were drawn from a list of densitometries (DXA) carried out in the Hospital of Torrevieja during the first quarter of 2009. Using simple random sampling 110 women were selected, of whom 90 participated in this study. The FRAX® tool was applied to all of them, recording the treatment for osteoporosis which they were following, and the service which had initiated the prescription. A value of >10% for the principal fracture, and a value of 3% for a hip fracture, were considered to indicate a high risk of fracture.

Results: Fifteen patients (16.66%) had a FRAX® index with a high risk of fracture. Only 23% of patients in treatment had a FRAX® index with a high risk of fracture. 40% of those patients with a high risk FRAX® index were not taking any specific treatment.

Conclusions: The use of the FRAX® tool may change the indication for treatment in many patients in whom the decision had been based only on bone densitometry.

Key words: *FRAX® index, treatment, osteoporosis.*

Introduction

The objective of all treatment for osteoporosis is the prevention of fractures both in the hip, due to the fact that they result in higher rates of mortality and disability, as well as osteoporotic fractures in other part of the skeleton due to their frequency and relationship with a reduction in survival rates and in the quality of life of the patient[1].

For many years, the main reference used to take therapeutic decisions has been the evaluation of densitometric values, given that on these have been based the guides which we have used since recently[2].

However, although bone densitometry continues to be considered as the test of choice for the diagnosis of osteoporosis and the principal predictor of fractures[3-6], it is unquestionably the case that it has limitations, making its use as the single factor in establishing treatment for the disease inadvisable.

Without a doubt, a fracture is a multifactorial outcome in which are involved factors which, along with age, influence the bone mass and architecture, in short bone resistance, such as the body mass index, history of other fractures, genetics, intake of pharmaceutical drugs, alcohol and tobacco habits, etc., added to which are "extra-bone" factors, which may be related to increased risk of falls, such as functional or visual deficiencies, intake of hypnotics, etc.

After significant clinical trials and major cohort studies, different combinations of these factors have generated the appearance of scales of risk: the National Osteoporosis Foundation (NOF) index, the Fracture Index, the Osteoporosis Risk Assessment Instruments (ORAI) test[7-8], etc. However, in each case the diversity of factors and the lack of a hierarchy within them has resulted in them seldom being used in normal clinical practice.

To facilitate the use of risk factors a team from the University of Sheffield, led by Professor Kannis and under the auspices of the WHO, created FRAX® (Fracture Risk Assessment Tool), a tool accessible over the internet which measures the absolute risk of suffering an osteoporotic fracture in the next ten years[9]. FRAX® is the result of a study of significant risk factors from a study of nine prospective populational studies, which analysed data from thousands of people.

The following risk factors are used in the calculation of the risk of fracture, although not all have the same strength of association: age, sex, body mass index, parental history of hip fracture, being an active smoker, treatment with glucocorticoids for more than 3 months, suffering rheumatoid arthritis, suffering metabolic disorders which provoke secondary osteoporosis, daily intake of more than three units of alcohol, to which may be added bone mineral density (BMD) measured in the femoral neck.

Using this data FRAX® will provide us with two values of absolute risk of fracture: Hip Fracture (HF), absolute risk of suffering a hip fracture in the next ten years; and Major Fracture (MO), for the combination of fractures in the humerus, wrist, vertebrae and hip; the quantitative value of the risk should be an essential element for the indication of a specific treatment for osteoporosis.

In spite of its limitations, the possibility of having available a tool which is easy to use, available on the web and capable of quantifying levels of risk, could be a great help when taking therapeutic decisions for patients with osteoporosis.

The objective of this study is to discover the risk of fracture in a group of patients of the Torrevieja Health Department with suspected osteoporosis, using the FRAX® tool in a simulated way, and to confirm whether the professionals in our department have adjusted to the recommendations extracted from the FRAX® values for the initiation of the treatment.

Patients and method

The patients were identified through bone densitometries (DXA) carried out in the radiological service of our hospital during the first quarter of 2009. During this period 1,108 tests were performed for the department, and, using a simple random sample of those performed in women, 110 patients were selected.

Between the months of May and June of 2009, the patients were contacted by telephone to ask their oral authorisation to participate in the study and an appointment made in the rehabilitation service for the completion of a questionnaire.

Five patients (4,54%) declined to participate in the study, two (1.81%) had an insoluble language barrier (they spoke neither English or Spanish), and thirteen (11.81%) could not be located.

In total, ninety patients made up the sample, fifty four of whom (60%) attended the hospital, with thirty six having problems of availability or transport, so the questionnaire was completed over the telephone (40%). In all the cases the following variables were recorded:

- Antiresorptive-osteoformative treatment for osteoporosis, with the possibility of their taking the following active compounds being evaluated: etidronate, alendronate, risedronate, ibandronate, raloxifene, calcitonin, strontium ranelate, teriparatide and PTH 1-84.
- The service to which the professional who initiated the treatment belonged.
- Risk of fracture using the FRAX® index, complementing this in all cases with the BMD in the femoral neck. The risk was considered to be high for a hip fracture when the HF value had levels equal to or higher than 3, and for a major fragility fracture, when the MO was higher than or equal to 10.

The study was authorised by the Research Committee of the Hospital of Torrevieja.

Statistical method

A descriptive statistical analysis was carried for each variable, obtaining the frequency distribution for the quantitative variables, the characteristic parameters were calculated: mean, standard deviation, maximum and minimum.

Results

The patients had an average age of 64.22 years (40-88 years), with a standard deviation of 11.24.

Thirty nine patients (43.33%) were receiving specific antiresorptive/osteoformative treatment.

With regards to the prescribing service, primary care was the service which indicated the treatment on most occasions, 20 (53%); followed by rehabilitation, 9 (23%); rheumatology, 8 (20%); the gynaecology and traumatology services having initiated the prescription on one occasion (2.5%).

Fifteen patients (16.66%) had a high risk of fracture according to the FRAX® index, with high parameters for HF and MO (Table 1).

In analysing the treatment adjusted to the risk factors according to FRAX® it was found that 23% of the patients treated had a FRAX® level indicating a high risk of fracture, and 40% of patients with a high risk of fracture did not receive treatment (Table 2).

Table 1: FRAX® share index

Major Osteoporotic		Hip Fracture	
≥ 10	≤ 10	≥ 3	≤ 3
15 (16.66%)	75 (83.44%)	15 (16.66%)	75 (83.44%)

Table 2: List of index patients and FRAX®

	FRAX without risk	MO ≥ 10 HF ≥ 3	Total
Treatment Yes	30 (40%)	9 (60%)	39
Treatment No	45 (60%)	6 (40%)	51
	75	15	90

No significant association appreciate

Discussion

Our study is a simulation of how therapeutic decisions may have been modified had the FRAX® tool been used before the initiation of treatment for osteoporosis, and, while it has clear limitations, such as the size of the sample and the fact that we applied the FRAX® tool in patients who had already initiated treatment, we believe that it reflects the reality of normal clinical practice.

In the results we obtained we can observe that if the criteria were to have been based on the FRAX® tool only 23% of the patients treated would have had to have initiated therapy; which is to say that 77% of the prescriptions would have been of dubious justification: figures much higher than those found by other authors[10], although it is possible that in some cases the presence of earlier fractures may have been the determining factor at the time of prescribing the treatment. What seems to us even more worrying is that 40% of patients with high risk of suffering an osteoporotic fracture according to the FRAX® index did not receive any antiresorptive/osteoformative treatment.

In short, if FRAX® had been taken as a reference the number of prescriptions would have been reduced significantly. However, we must admit that FRAX® is not a perfect tool and, from its inception, it has been accused of having some defects, such as not evaluating the BMD in the spinal column, the intake of calcium, levels of vitamin D, or the frequency of falls, among other factors, which may result in it underestimating the risk of fractures[11-13]. In addition, there is not yet a single clinical trial published which demonstrates that the tool is useful in the prevention of fractures.

Another difficulty, of a local nature, is that there is no recognised cut off point for therapeutic intervention for Spain. In our study we have used the values of 3% for absolute risk of hip fracture and 19% for major osteoporotic fractures, since it is the lower cut off value communicated by Spanish authors[14,15].

In spite of its limitations, we are of the opinion that the introduction and dissemination of FRAX® will provide a good tool to support therapeutic decision-making, since it is able to quantify the weighting of the different risk factors. Its ease of use, accessibility on the web and clarity could result in its rapid inclusion in normal clinical practice, something which has not happened with other indices, and the more than 55,000 daily visits is indicative of its massive use.

In addition, this tool is able to correct an anomaly caused by the excessive weight given to densitometry when prescribing antiresorptive/osteoformative drugs, which tends to concentrate treatment on younger patients, where the risk of suffering fractures, in spite of their having osteoporotic values, is low[16,17].

This situation could cause a range of problems, one of which would be the cost to the health system, due to a significant change in cost-benefit, or the possible abandonment of treatment in older age, precisely when the risk of fracture is highest, either by boredom or by potential adverse effects provoked by prolonged periods of therapy, such as a deterioration in bone quality and the appearance of atypical fractures, which are attributable to long periods of treatment with biphosphonates[18-21].

The work of disseminating the importance of risk factors, and in particular the use of the FRAX® tool should be carried out in all specialisms which usually treat patients with osteoporosis, especially among primary care doctors, since in some health regions, as in our case, they play a major role in this pathology.

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The author declares that there is no conflict of interest.

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Patient with fracture due to postmenopausal osteoporosis in Spain: medical care pathway

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Summary
Background: In Spain, the flow of medical care for a patient with a fracture due to postmenopausal osteoporosis (PO) in the hospital system is not understood. A literature review has been carried out in order to define the hospital care pathway for patients with fracture due to PO in normal clinical practice, taking into account the different medical specialisms involved. In addition, it was attempted to determine the role of each specialist and the most common referral services.
Material and methods: The databases PubMed/Medline, ISI Web of Knowledge, EMBASE and Google Scholar; IBECS (Spanish Bibliographical Index in Health Sciences (Índice Bibliográfico Español en Ciencias de la Salud)) and MEDES (Medicine in Spanish (Medicina en Español)) were consulted, as well as the web pages of the Spanish Society of Rheumatology, the Spanish Society for Bone and Mineral Metabolism Research, the Spanish Society of Orthopaedic Surgery and Traumatology, and the Spanish Association for the Study of the Menopause, to identify publications appearing between 2000 and 2010 in English or Spanish. The principal national clinical practice guides (CPG) for PO were reviewed.
Results: A total of 114 articles were identified. After discounting non-relevant publications, duplicate publications and those published in languages other than English or Spanish, 13 articles were selected. 4 articles were excluded (n=2 screening for osteoporosis, n=1 risk factors, n=1 cost studies), with a total of 9 articles being reviewed. All the articles were international (n=9), including American (n=4), Canadian (n=2), Swiss (n=1), Irish (n=1) and multinational (n=1), and described the outpatient management of fractures due to PO mainly in the extra-hospital environment. Notable in this environment is the essential role of the orthopaedic surgeon and the need for their coordination with family doctors to guarantee the optimum follow up of patients and the prevention of second fractures. The CPGs reviewed referred only to the diagnosis and therapeutic management of the patient with PO. No information was found on referral services, or on the role of each specialist in the management of these patients.
Conclusions: The care pathway for patients with osteoporotic fracture, and which professionals are involved, are poorly described in the literature, both nationally and internationally. The clinical management of patients with fracture due to osteoporosis in hospitals is an area of healthcare which needs description and analysis.

Key words: *postmenopausal osteoporosis, osteoporotic fracture, management of the disease, bibliographical review.*

Introduction

Osteoporosis is a disease characterised by a reduction in bone mass and changes in the microarchitecture of bone tissue which result in an increase in fragility, and consequently, a high risk of fractures[1]. These may occur in any part of the skeleton, although the areas most affected are the spinal column, the distal radius (Colles fracture) and the hip[2]. It has been estimated that a woman of 50 years of age has a 40% risk of suffering a fracture during the rest of her life, while in men this risk is 13%[2].

Osteoporosis is the most prevalent disease of bone, affecting 35% of Spanish women over 50 years of age, a percentage which rises to 52% in those over 70 years of age[3]. One in every 5 women aged over 50 has at least one vertebral fracture due to osteoporosis, which is associated with a deterioration of health-related quality of life and an increased risk of suffering other fractures. The annual incidence of femoral fracture in women over the age of 50 years is 3 per 1,000, while the incidence of fracture of the distal forearm is nearly twice that[3]. In Spain there are 90,000 hip fractures and 500,000 vertebral fractures per year linked to osteoporosis, according to the Spanish Rheumatology Society (SER) in its III Document on Osteoporosis[4]. The incidence of hip fracture in Spain varies between 34.9 and 83 fractures per 1,000 inhabitants[5].

According to a survey, aimed essentially at outpatients, on the management of resources in osteoporosis, we found that professionals involved in its treatment included, amongst others, rheumatologists, endocrinologists and traumatologists[6]. Especially notable was the role of the endocrinologist and traumatologist in its diagnosis, with special emphasis on the role of the latter after the appearance of the first fractures. The gynaecologist and the doctor of internal medicine, on their part, play an essential role in the diagnosis of postmenopausal osteoporosis (OP). What is not known, however, is the role of these, and other specialists, in the management of the patient with fracture due to postmenopausal OP in the hospital setting, and how each of them is linked in the medical care pathway for this group of patients in Spain.

Objectives

Principal

To carry out a systematic literature review on the care pathwayfollowed by patients with fracture due to OP in normal clinical practice in a hospital setting, especially taking into account the different medical specialisms involved.

Secondary

To determine how each specialism influences the hospital care pathway followed by these patients, and to describe which are the most common referral services in and from the hospital.

Methodology

Selection criteria

The criteria for including articles were those:

- Referring to patients with OP and fracture.
- Related to the clinical management of this pathology.
- Which were National and international.
- Carried out in a single centre or multiple centres.
- Published between January 2000 and May 2010.
- In English or Spanish.
- Which were national clinical guides.
- Which were systematic literature reviews.

Excluded were:

- Clinical trials, due to the experimental context in which they are developed.
- Articles referring to the prevention and diagnosis of OP.

Search strategy

To identify the most relevant studies to be included in the bibliographical review, a search was made of the following: Pubmed/MedLine database (including the Medex and Ibecs databases). ISI Web of knowledge (including the Web of Science, Current Contents Connect ISI Proceedings, Derwent Innovations Index, Journal Citations Report, Essential Science Indicators), Embase and the grey literature in Google Scholar, as well the bibliographical reference lists in the articles selected.

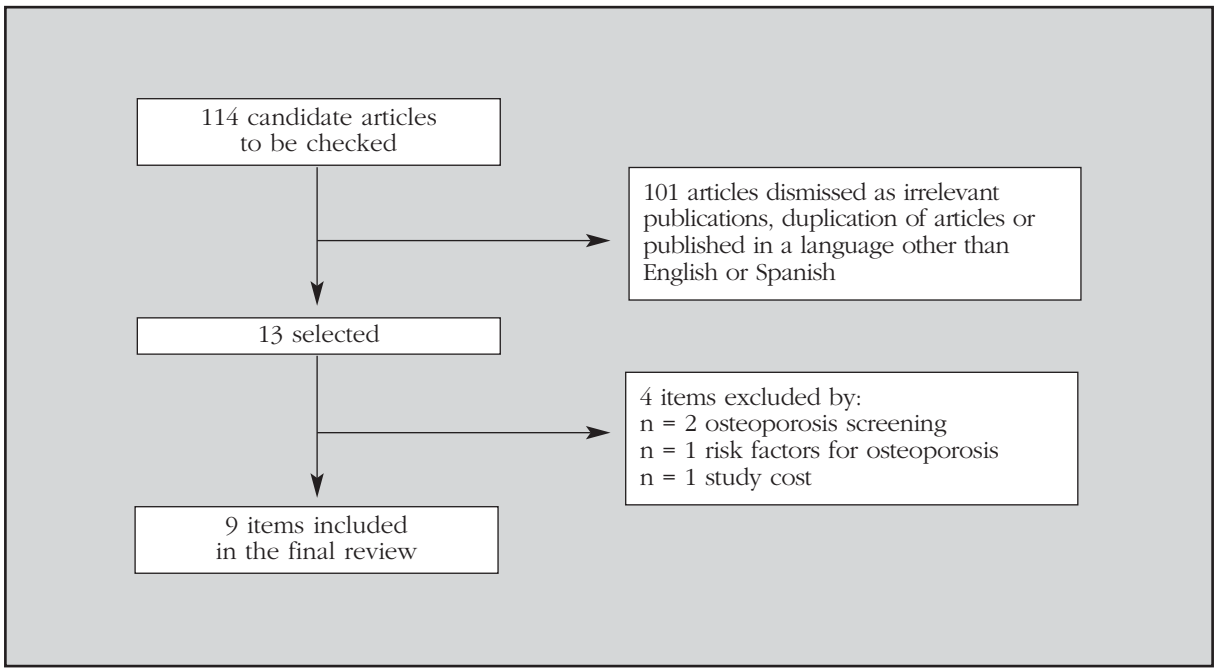
In **Pubmed** various combinations of Mesh terms were used:

- Search 1: “postmenopausal osteoporosis" [Mesh] AND "practice management" [Mesh] OR "medication therapy management" [Mesh]) OR “management quality circles” [Mesh] OR “patient care management” [Mesh] OR “Disease management” [Mesh] AND “fracture” [Mesh] (73 articles).
- Search 2: “postmenopausal osteoporosis” [Mesh] AND “fracture” [Mesh] AND “Spain” [Mesh] (10 articles).
- Search 3: “postmenopausal osteoporosis management” AND “fracture” (616 articles).
- Search 4: “postmenopausal osteoporosis management” AND “fracture” [Mesh] AND “costs” [Mesh] (35 articles).
- Search 5: “physicians practice patterns” [Mesh] AND “professional practice” [Mesh] AND “postmenopausal osteoporosis” (6 articles).
- Search 6: “hospital” [Mesh] OR “medication systems, hospital” OR “medical staff, hospital” [Mesh] AND “postmenopausal osteoporosis” [Mesh] (12 articles).

The following terms were used in the search with the **ISI Web of Knowledge:**

- Search 1: “postmenopausal osteoporosis management” [AND] “fracture” [AND] “hospital” (41 articles).
- Search 2: “postmenopausal osteoporosis management” [AND] “fracture” [AND] “professional practice” (1 article).

Figure 1. Results of literature search



The terms used for the **EMBASE** search were:
- Search 1: "after or follow" AND "fragility or osteoporosis" AND "fractures" (89 articles).
- Search 2: "practice and pattern" OR "practice and management" AND "fragility or osteoporosis" AND "fractures" (20 articles).
- Search 1 OR Search 2 (107 articles).
- Duplicates (63 articles).
- Year limited to, "2000-2010" (60 articles).
- Limited to "English or Spanish" (46 articles).

The search strategy for the **IME** database **(Índice Médico Español)**:
- Search 1: "osteoporosis" AND "hospital" (2 articles).
- Search 2: "osteoporosis" AND "manejo" (4 articles).
- Search 3: "osteoporosis" AND "servicio" (3 articles).
- Search 4: "osteoporosis" AND "derivación" (1 article).

In addition, in the Google Scholar database a search was carried out using the terms "practice patterns in postmenopausal osteoporosis and fracture" "postmenopausal osteoporosis fracture intervention". The following local databases were also explored: IBECS (Índice Bibliográfico Español en Ciencias de la Salud) and MEDES (Medicina en Español) applying similar search terms in Spanish.

The web pages of the following scientific societies were also reviewed: the Spanish Society of Rheumatology (SER), the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM), the Spanish Society for Orthopaedic Surgery and Traumatology (SECOT), the Spanish Society of Gynaecology and Obstetrics (SEGO), and specifically, the Spanish Association for the Study of the Menopause (AEEM).

Results

The search showed up a total of 114 articles as candidates for review. After discarding non-relevant publications, duplicated articles and those published in a language other than English or Spanish, 13 articles were selected. 4 articles were excluded for various reasons (n=2: osteoporosis screening, n=1 risk factors for osteoporosis, n=1: costs study) (Figure 1).

All the articles selected are international (n=9) and mostly describe the medical care pathway in the management of the follow up to fractures in women with OP, mainly in an extra-hospital setting (Table1). American (n=4), Canadian (n=2, Swiss (n=1), Irish (n=1) and multinational (n=1) studies were identified. The most common methodology used interviews or surveys of professionals (n=4) in which the perspectives of medics involved in the management of osteoporosis, above all orthopaedic surgeons, were explored, Algorithms for clinical-therapeutic activity were also suggested (n=2) as well as barriers identified to the optimum treatment of the patient with fracture due to OP (n=2). In only one article (n=1) was there a reference to the implementation of a clinical care pathway for patients with osteoporosis. In the sources consulted no articles were identified which referred specifically to the medical care

pathway in hospital of the patient with fracture due to OP. Below, we describe the principal data obtained from each of the articles reviewed, broken down by country:

Articles selected

1.- International multicentred

A multinational survey was carried out of 3,422 orthopaedic surgeons in France, Germany, Italy, Spain, United Kingdom and New Zealand with the objective of exploring the degree of involvement of orthopaedic surgeons in the identification, evaluation and treatment of patients with osteoporosis[7]. The majority of those surveyed in all countries considered that the orthopaedic surgeon is the professional who should identify and carry out the management of osteoporosis in patients with fracture. In addition, if a fracture due to osteoporosis was suspected, the majority of the surgeons in France, United Kingdom and New Zealand would refer the patient to a specialist in osteoporosis or to the family doctor, while more than 80% of the participants in Germany and Italy reported that they themselves followed up the patient. It was observed that half the surgeons surveyed received little or no information on the treatment of patients with osteoporosis.

2.- United States

Skedros et al.[8] carried out a survey 107 orthopaedic surgeons in relation the management of patients with osteoporosis. The survey was carried out with the objective of evaluating the opinions and principles of the orthopaedic surgeons in relation to the treatment of patients with osteoporosis, and patients with osteoporosis and fracture. The results showed that the surgeons preferred to refer those patients treated for osteoporotic fractures to primary care doctors to carry out monitoring of the medication used by the patient, and emphasised the importance of ensuring treatment over time to prevent second fractures.

Another study which was developed with the objective of determining if orthopaedic surgeons referred patients with fracture to the primary care (PC) doctor for monitoring effectively described the role of the orthopaedic surgeon in the diagnosis and treatment of osteoporotic fracture[9]. A programme of intervention was suggested to facilitate coordination between orthopaedic surgeons and doctors in PC for the preventative treatment of secondary osteoporotic fractures. The programme proposed carrying out the following actions: 1) a programmed visit to the PC doctor (after less than 4 weeks have elapsed); 2) the initiation of the monitoring of the patient's bone metabolic state; 3) to propose a date for the performance of densitometry; and 4) education in the prevention and treatment of osteoporosis and osteoporotic fractures. The authors highlighted the fact that in other hospitals in the United States, for example, protocols were used in which patients with hip fracture with strong suspicion of OP have a visit to the doctor of internal medicine or endocrinologist, or the family doctor and/or have a personal visit from a nurse specialising in orthopaedic surgery to monitor the patient and supervise the medication used.

Feldstein et al.[10] made a study in which interviews and focus groups were carried out to evaluate the management of osteoporosis after a fracture by the specialists involved. It concluded that, in spite of the orthopaedic surgeons recognising that they should play a more active role in the monitoring of this type of patient, the reality is that they are limited to the active treatment of the fracture, without considering the monitoring of the osteoporotic patient. Both the family doctors and the specialists agreed on the necessity of imposing standard protocols which would involve the different professionals (orthopaedic surgeons, radiologists, casualty staff) in the management of osteoporosis at the time of fracture. In addition, the specialists ought to be provided withbasic training in relation to osteoporosis and the carrying out of its diagnosis and treatment, while the family doctor would be responsible for the monitoring and prevention of second fractures.

In relation to the professionals involved in the management of women with OP and forearm fractures, a retrospective study found that during the first 6 months the majority of patients were seen by a doctor as well as by an orthopaedic surgeon[11]: 69% by a doctor of internal medicine or family doctor, 4% by another specialist (gynaecologist or endocrinologist), 2% by both specialists, while 25% only had visited an orthopaedic surgeon 12 months after the fracture. 12% of the participants were recommended to start preventative drug treatment, while 5% were already receiving specific treatment for osteoporosis at the time of the fracture.

3.- Canada

Elliot-Gibson et al.[12] carried out a systematic review in which articles were selected which described the activity pathways in the diagnosis and treatment of OP after a pathological fracture. One of the aspects explored was the barriers which exist to the investigation and treatment of OP. Primary care doctors in Canada and Ireland[13,14] described the principal barriers to the initiation of preventative treatment as the difficulty in carrying out densitometry during the follow up and the lack of time to refer patients for secondary prevention. In this work it is suggested that that the development of an algorithm based on clinical guides is an important step in ensuring the correct management of patients with pathological fracture.

4.- Switzerland

Chevalley et al.[15] developed the Osteoporosis Clinical Pathway, with the aim of controlling health costs related to the disease, without altering the quality of the medical care. Any hospitalised patient or out-patient with a recent low energy fracture was considered as a candidate to enter the pathway. The pathway includes three differentia-

Table 1. Articles selected in the bibliographic review

Author, Year publication	Country	Objectives	Principal results of interest for the search
McKercher HG, 2000	Canada	Survey carried out in doctors in Ontario in relation to their role in the diagnosis and treatment of osteoporosis	The main barriers to the initiation of treatment were the cost of the therapy, the rejection by the patient of the initiation of the treatment and the time and cost of diagnosis
Sheehan J, 2000	Ireland	To evaluate the variation in clinical practice of orthopaedic surgeons in relation to the preventative treatment related to fracture of the femur	It was concluded that it is necessary to have a clear definition of the roles, and that local protocols needed to be developed
Chevalley T, *et al.* 2002	Switzerland	To design a clinical pathway for osteoporosis for the therapeutic management of patients with low energy impact fracture	A clinical pathway may help in the identification of patients with osteoporosis in a high risk population, providing support both to orthopaedic surgeons and family doctors in the diagnosis and treatment of the disease
Cuddihy MT, 2002	U.S.	To identify the determining factors in the treatment of OP after a distal forearm fracture	12 weeks after the fracture 83% had visited a doctor (excluding the orthopaedic surgeon). 17% received treatment with drugs for osteoporosis
Elliot-Gibson V, 2004	Canada	Systematic review of clinical practice in the investigation and diagnosis of OP in women and men with fracture due to fragility	The main barriers encountered were: the cost of the therapy, time and cost of the resource used for the diagnosis, doubts related to the medication, and ambiguity regarding the person responsible for taking on the management of this pathology
Skedros JG, 2004	U.S.	To determine if orthopaedic surgeons effectively refer patients with osteoporotic fracture to primary care for monitoring of treatment	A total of 43.5% of the patients did not visit a family doctor until 84 days had lapsed since the fracture. The use of antiresorptive medication was only initiated in 53.8% of patients
Dreinhöfer KE, 2005	France, Germany, Italy, Spain, United Kingdom, New Zealand	Survey regarding the management of osteoporotic fracture	Less than a fifth of those specialists surveyed had referred a patient being treated for fracture for the performance of densitometry, while 20% disclosed that they had never done so
Skedros JG, 2006	U.S.	Survey of 171 orthopaedic surgeons	68% of those surveyed considered it appropriate to take the role of prescribing treatment for osteoporosis, 74% preferred to administer biphosphonates, and more than 77% preferred to administer calcium and vitamin D supplements
Feldstein AC, 2008	U.S.	To evaluate the different perspectives in the management of osteoporosis after fracture	Both family doctors and specialists agreed on the necessity of imposing standardised protocols which would involve the different professionals (orthopaedic surgeons, radiologists, and casualty staff) in the management of osteoporosis at the time of fracture

ted steps: in the first step the nurse gathers the patient data, mainly related to risk factors, such as previous fracture, the level of the patients understanding of their disease, the relationship between the fracture and the disease, calcium and protein intake. In the second step the doctor supervising the programme may carry out densitometry and/or biochemical tests to discount secondary osteoporosis, or refer to a specialist in bone metabolic diseases those patients with a complex medical history and/or other diseases. It is important to mention that throughout the pathway there is constant communication between the orthopaedic surgeon and/or family doctor and the doctor and/or nurse supervising the programme. The last step of the pathway consists of the therapeutic recommendations which the orthopaedic surgeon transmits to the family doctor responsible for monitoring the patient. In conclusion, this algorithm would facilitate the pathway being followed by the orthopaedic surgeon and/or the primary care doctor in the management of patients with osteoporosis while, as the article's authors explain, the cost-effectiveness of the algorithm needs to be demonstrated in further studies.

National guides to clinical practice: do these reflect the intra-hospital care pathway after an osteoporotic fracture?

With the aim of reflecting the theoretical recommendations for the management of this type of patient we have reviewed the national clinical practice guides for patients with OP.

Only the "Practical guide to primary care activity: osteoporosis in the Community of Valencia"[16] describes the referral criteria for a patient suspected of having an osteoporotic fracture, which if acute would refer the patient to traumatology, while if the fracture is not acute, the treatment would be referred to the primary care doctors. Subsequently the patient would end up being referred to rehabilitation in both cases. The hospital pathways used in the care of patients with postmenopausal osteoporotic fractures are not described, nor are the medical specialisations involved (Figure 2).

The Working Group of the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM)[17] described in the clinical practice guide they published concerning OP an activity algorithm in patients with vertebral and non-vertebral fracture. Although it makes reference to the recommended clinical management of these patients the guide to clinical practice makes no recommendations as to what should be deployed in the intra-hospital pathway for the management of patients with postmenopausal osteoporotic fractures.

The Spanish Society of Internal Medicine has published an activity protocol for osteoporosis. However, the Guide to Clinical Practice for osteoporosis published by the Spanish Society for Orthopaedic Surgery and Traumatology[19] highlighted the role of the orthopaedic surgeon in the diagnosis and treatment of patients with fracture due to osteoporosis. It does not describe the care pathway which should be followed in this type of patient.

Finally, the Spanish Society for Gynaecology and Obstetrics in their guide published on the menopause and postmenopause[20] mainly focus on the risk factors for fracture in postmenopausal women and the principal treatments indicated in this type of patient. The hospital management of patients with postmenopausal osteoporotic fracture is not specified in this guide. Recently, the AEEM published the "Guide to Clinical Practice for Osteoporosis in Gynaecology"[21], which mainly addresses the role of the gynaecologist in both the prevention and management of osteoporosis. This guide, also, does not reflect the intra-hospital pathway which is followed in real-world practice with this type of patient.

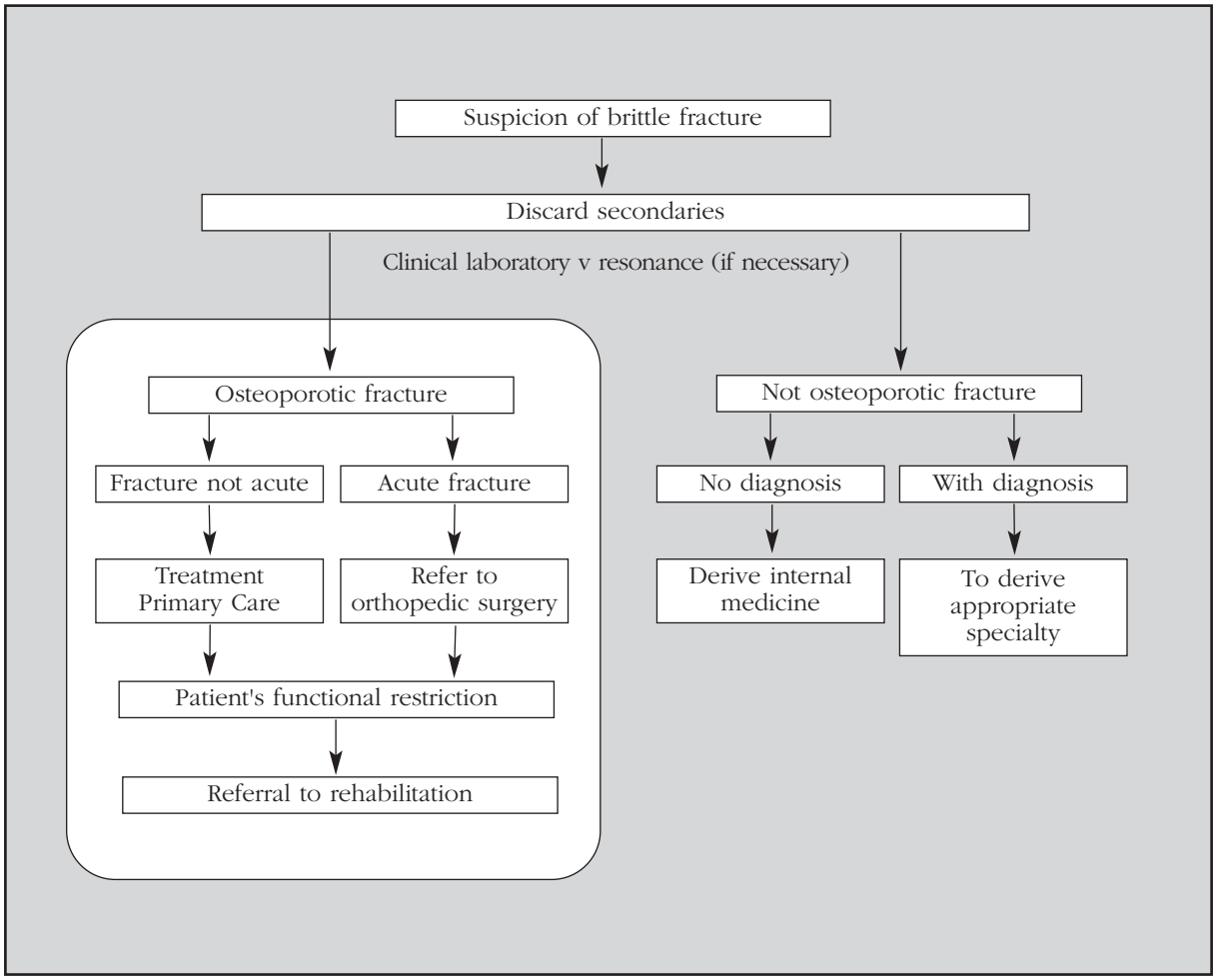
The guides described, although they refer to the management, diagnosis and therapy for the patient with OP, do not make recommendations regarding the care process or the medical professions which should be involved in the management of patients with fracture due to OP.

Discussion

The literature published regarding the medical care pathway and the professions involved in the management of patients with osteoporotic fracture is limited. With respect to the extra-hospital environment, what stood out in the articles reviewed was the essential role of the orthopaedic surgeon, inferring the necessity of coordinating their activity with that of the family doctor to guarantee the most appropriate follow up of those patients and the prevention of second fractures. However, in the sources consulted, there were no publications which described, for example, the care pathway followed by a patient with a fracture due to OP in the hospital setting in our country.

There is also little literature which describes the key actions in the management of the disease, such as the lapsed time from the diagnosis to the referral of the patient with OP and fracture. We have identified as one of the common challenges in the management of multifactorial chronic pathologies, such as OP, the multidisciplinary character of its care, with a number of specialists involved. The articles selected reflect the fact that the majority of patients visit other doctors in addition to the orthopaedic surgeon after an osteoporotic fracture, including a doctor of internal medicine or a family doctor, as well as other specialist such as gynaecologists or endocrinologists, but without there being clear referral criteria. The review also showed that the follow up is, in many cases performed by the specialists in traumatology or gynaecology, and in a small percentage (12%) by the family doctor. In spite of the fact that the professional who initially treats the patient is the orthopaedic surgeon, the lack of standardisation in the roles of each of the professions involved in a treatment, meant greater delay for this type of patient[9].

Figure 2. Referral criteria in a patient with suspected fragility fracture (Primary Care)



As we have seen, there are various management patterns with this pathology which differ as a function of the country under consideration. For example, Dreinhöfer et al.[7] found that in 5 different countries, the majority of orthopaedic surgeons were focussed on the surgical treatment of fractures, while in other countries such as, for example, Germany, most of the orthopaedic surgeons, in also having a working role outside the hospital setting treating patients with diverse musculo-skeletal pathologies, cover the more clinical aspects of the follow up of the patient with fracture due to postmenopausal osteoporosis.

The articles referring to surveys carried out with orthopaedic surgeons show that these professionals are key in the achievement of an increase in the rate of identification and treatment of osteoporotic fractures. However, studies reviewed by Elliot-Gibson et al.[12] indicate that some orthopaedic surgeons consider that the clinical management of this type of patient is the responsibility of other specialists. Various orthopaedic organisations participate actively in increasing the identification of postmenopausal osteoporosis and in improving the treatment of this type of patient.

In Spain there is no literature which describes the medical care pathway for patients with postmenopausal osteoporotic fracture. In spite of including Spanish databases, the articles did not include algorithms for clinical action protocols which should be followed with a patient with an osteoporotic fracture. With the information currently available it is not practicable to describe the influence of each specialism involved in the care of these patients, or the most common referral services. Carrying out of studies which explore these aspects would enable a more homogeneous and standard management of this pathology. Information which it would be useful to discover would be the lapsed time from when the patient suffered the fracture up until the initiation of treatment and monitoring, due to the importance this matter has in the patient's perception of the quality of care they receive.

The national clinical practice guides reviewed do not make explicit the activity algorithm to be

followed with a patient with osteoporotic fracture in a hospital setting, making mention almost exclusively of the pharmaceutical guidelines to be used. The development of guides which describe the care pathway for this type of patient in the hospital setting, the referral criteria, and the roles of each of the professionals involved, would enable a better management of the pathology and its complications.

Two fundamental limitations should be taken into account when the conclusions of this study are interpreted: firstly, the study does not review the internally disseminated clinical process protocols or clinical process algorithms in hospitals in the Spanish health system, and which very probably exist in many of them. Secondly, only articles in Spanish or English are included, omitting publications in any other language, although Spanish databases have been consulted which essentially prioritise the appearance of national articles.

We consider that this study provides information on the current state of play in this matter and defines an area of healthcare in the Spanish hospital sector in need of study and dissemination, i.e. the management of patients with OP-related fracture and the professional disciplines involved in it.

Conclusions

According to the sources consulted, there is little (or no) descriptive information on the care pathway followed by a patient with osteoporotic fracture, or regarding the professionals involved, at either a national or international level. It is opportune, in the absence of a review of internally disseminated hospital guides, to highlight the need to carry out observational studies which reflect the care pathway followed by this type of patient in the hospital setting.

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Conflict of interest: The study was sponsored by Amgen S.A. Dr Núria Márin works for Amgen S.A. Dr Luís Lizán works for Outcomes´10 and Drs Blanch and del Pino are specialists who carry out most of their work in the Spanish public health system.

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Osteonecrosis of the jaw associated with the use of oral biphosphonates: apropos five cases

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Summary
Osteonecrosis of the jaw is a disease which needs to be taken into account whenever there is exposure of bone as a secondary result of any dental operation in a patient who has been taking biphosphonates over a long period of time. Unknown until the last few years, knowledge of such a pathology has increased due to the current increase in the taking of biphosphonates in the population, with most of the published cases being related to the taking of biphosphonates intravenously. We present 5 clinical cases of osteonecrosis of the jaw associated with the use of oral biphosphonates.

Key words: *osteonecrosis of the jaw, biphosphonates, alendronate, ibandronate.*

Introduction

Osteonecrosis of the jaw (ONJ) is characterised by an ulcerated lesion in the oral mucosa with exposure of bone for a period of longer than 8 seeks, located in the jaw and associated with the use of oral and intravenous biphosphonates in the absence of cervicofacial radiotherapy[1-3].

Since 2003, with the appearance of the first clinical cases of ONJ in the literature, there have been numerous publications regarding the development of this pathology[4-6], the majority of these secondary to therapies with intravenous biphosphonates, associated, in turn, with different chemotherapy and radiotherapy treatments.

In this article we bring together a series of 5 cases of ONJ related to the taking of oral biphosphonates, and carry out a bibliographic review of the pathology and management of the patient taking oral biphosphonates who is going to undergo oral surgery.

Clinical cases

We present 5 cases of ONJ in relation to the use of oral biphosphonates seen in our service during the years between 2005 and 2008 (Table 1). They all have as common antecedents dental surgery and the taking of oral biphosphonates at the time of the diagnosis of ONJ.

Case number 1. Woman of 70 years of age diagnosed with early osteoporosis due to an earlier hysterectomy which was treated with ibandronic acid over a period of 4 years. She developed a clinical picture characterised by pain and tumefaction in the submaxillary cells and inferior vestibule compatible with grade III ONJ. She was treated surgically by the elimination of the sequester, curettage and local advancement flaps to close the lesion, associated with intravenous antibiotic treatment with amoxicillin clavulanate 1g/200 mg every 8 hours for two week, plus 100 mg of doxycycline orally every 24 hours for 14 further days (Figures 1 & 2).

Case number 2. Patient with history of arthrosis of the knee (with knee prosthesis) recurrent polychondritis in treatment with corticoids and type II, or senile osteoporosis. The patient had received alendronate orally over a period of 4 years, developing grade II ONJ. She was subsequently treated with intravenous antibiotherapy consisting of amoxicillin clavulanate 1g/200 mg every 8 hours for a total of three weeks

Cases number 3, 4 and 5. The last three patients were women diagnosed with senile osteoporosis (one of them with history of rheumatoid arthritis treated with corticoids and immunosuppressants) and treated with oral alendronate (for three, five and four years, respectively), who developed ONJ grade III. They were treated by curettage of the lesion combined with intravenous antibiotherapy using amoxicillin clavulanate 1g/200 mg every 8 hours for a minimum period of 2 weeks.

All the patients had a complete remission of the lesions.

Discussion

ONJ was defined as such in the year 2007 by the American Society for Bone Mineral Research (ASBMR)[1] as an entity characterised by three requirements: previous taking of biphosphonates, presence of exposed or necrotic bone in the maxillary region which has been developing or more than 8 weeks, and the absence of radiotherapy in this area.

Traditionally, ONJ has been related to the use of intravenous biphosphonates in patients with history of neoplasms with metastasis, its secondary appearance related to the use of oral biphosphonates being rare. In the last few years, the growth in the use of oral biphosphonates in the treatment of osteoporosis has increased the number of cases of ONJ described[7]. In certain pathologies, such as rheumatoid arthritis, in which the development of serious osteoporosis has necessitated the initiation of treatment with oral biphosphonates, the appearance of ONJ has also been observed[8]. It has been determined that the risk of ONJ due to oral biphosphonates is related to the duration of treatment (above all, if it is greater than 3 years)[9]. In the cases described in this clinical note a period of approximately 3 or more years of treatment with biphosphonates was observed before the appearance of ONJ.

Within the group of biphosphonates associated with the development of ONJ, zoledronic acid is that which has resulted in most cases of ONJ[10,11]. Woo et al.[6], in a systematic review of 368 cases of ONJ observed that the oral biphosphonate which most frequently produced ONJ was alendronate, which agrees with our review. If we compare oral biphosphonates with intravenous it is seen that the intravenous administration develops ONJ more rapidly. Lazarovici et al., in 2011[11] studied 27 patients who had ONJ concluding that the average time for its appearance was 60 months for those who had taken alendronate, 13 for zoledronic acid and 35 months for pamidronate. Etiopathogenically, there is a series of factors which may explain the development of ONJ[2]. These are: changes in immunity and the neoplasm repair mechanisms, vascular compromise (in the same way as happens in other areas such as the hip and half-moon bone, essentially), low bone turnover, and toxicity in the bone[12] and other soft tissues of the biphosphonates themselves[13].

ONJ is characterised clinically by areas of exposed bone accompanied by fistulation, pain, paresthesia, dental movement, and even fracture of the jaw. In 65% of cases we find mandibular affectation, in 25%, affectation of the upper jaw and in approximately 10% bimaxillary affectation[6].

In most cases the prognosis is favourable, with ONJ due to oral biphosphonates having a better prognosis than those cases caused by intravenous biphosphonates[11]. The latter is aggravated by the deteriorated physical state of these patients (previous treatment with chemotherapy and/or radiotherapy).

The treatment for ONJ is based on the grade of ONJ which is diagnosed[5] (Table 2). In ONJ grade I the treatment of choice is rinsing with 0.12%

chlorhexidine; in grade II the first treatment needs to be associated with oral or intravenous antibiotherapy; and finally, in grade III, to those measures already mentioned should be added surgical treatment.

Therefore, the most important thing is to decide on how to manage the patient who is submitted for mouth surgery and who is being treated with oral biphosphonates over a long period of time. For De Souza et al.[14] it was necessary to postpone surgery and refer the patient to a specialist (rheumatologist or traumatologist) to evaluate the suspension of the biphosphonate and, even to substitute it for another medicine for the treatment of osteoporosis before surgery.

On the other hand, the American Society, in 2009, developed a protocol for the management of patients taking oral biphosphonates and who require a surgical intervention which involves the manipulation of the maxillary bones[9]:

- In patients whose treatment with oral biphosphonates has lasted less than 3 years and with no risk factors, it is not necessary to take any special measures.

- In patients whose treatment with oral biphosphonates has lasted for less than 3 years and who are taking corticoids concurrently it would be necessary to stop the oral biphosphonate treatment at least 3 months before surgery, if the systemic conditions of the patients allow it. The oral biphosphonates may be reintroduced once the bone is healed.

- In patients whose treatment with oral biphosphonates lasts longer than 3 years, independently of having taken oral corticoids or not, the taking of biphosphonates should be stopped at least 3 months before surgery if the systemic conditions of the patient permit. The administration of biphosphonates would be restarted only when the bone had healed.

Similarly, the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM) and the societies related to bone mineral metabolism have produced a document on the management of ONJ and the biphosphonates used in the treatment of osteoporosis[2]:

- In patients taking biphosphonates for less than 3 years and without risk factors it is not necessary to delay surgery

- In patients taking biphosphonates for less than 3 years and associated corticotherapy the biphosphonates should be discontinued three months before surgery, except where there is a high risk of fracture (age > 70 years, presence of earlier fracture, bone densitometry with a T-score of <-2.0). It would be reintroduced once the healing had occurred.

- With patients who are taking biphosphonates for more than 3 years the biphosphonates should be discontinued 3 months before surgery, except if there is a high risk of fracture (age > 70 years, presence of previous fracture, bone densitometry with a T-score <-3.0). It would be reintroduced once healing had taken place.

Figure 1. Orthopantomography and TAC which shows osteonecrosis in the right mandibular body

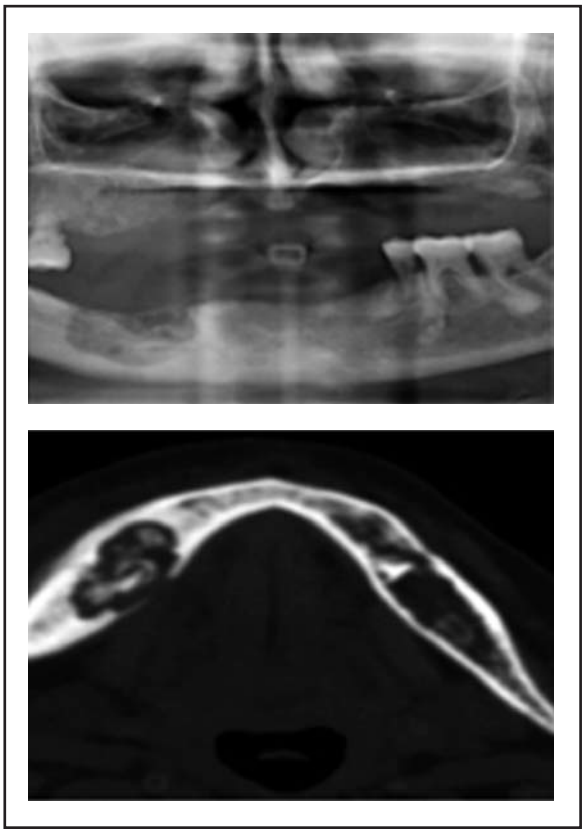
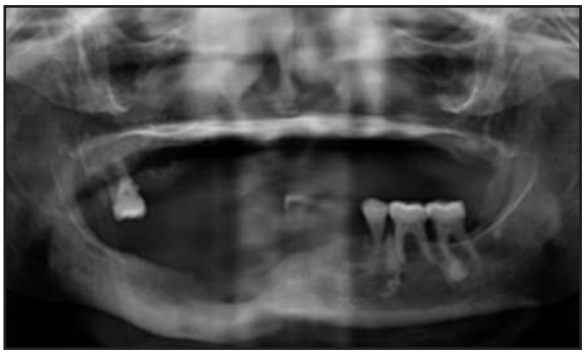


Figure 2. Control orthopantomography in which is seen the satisfactory development of bone re-ossification of the osteonecrosis in the mandible



Therefore, and in conclusion, ONJ is a little-understood but increasingly frequent pathology related to the taking of oral biphosphonates. New protocols and consensuses around the activity in relation to a patient taking oral biphosphonates over the long term and who is going to have oral surgery, will in future be the determining factor in avoiding, as much as possible, the development of ONJ.

None of the authors has a conflict of interest.

Table 1. Data from patients taking oral biphosphonates who develop ONJ (iv: intravenous therapy)

	Sex	Age	History of interest	Bisphosphonate oral	Cause of treatment	Duration of treatment	Stadium ONJ	Treatment
Case 1	F	70	Bronchial asthma, dental extraction	Ibandronic acid (150 mg monthly)	Postmenopausal osteoporosis	4 years	III	Bone curettage + iv antibiotherapy
Case 2	F	75	Recurrent polychondritis, dental extraction	Alendronate (70 mg weekly)	Senile osteoporosis	4 years	II	iv antibiotherapy
Case 3	F	81	Bronchial asthma, dental manipulation	Alendronate (70 mg sweekly)	Senile osteoporosis	3 years	III	Bone curettage and exodontia + iv antibiotherapy
Case 4	F	76	Rheumatoid arthritis, dental extraction	Alendronate (70 mg weekly)	Senile osteoporosis	5 years	III	Bone curettage + iv antibiotherapy
Case 5	F	74	Dental manipulation	Alendronate (70 mg weekly)	Senile osteoporosis	4 years	III	Bone curettage + iv antibiotherapy

Table 2. Stages of ONJ according to the American Society of Oral and Maxillofacial Surgery[9]

	Exposure of necrotic bone	Pain and signs of infection	Fistula and clinical or radiographical evidence of sequestered bone
Degree I	Yes	No	No
Degree II	Yes	Yes	No
Degree III	Yes	Yes	Yes

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Annual cost of the drugs used in the treatment of osteoporosis after a review of the reference prices

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Sir:
In a review of the role of zoledronic acid in the treatment of osteoporosis published in a monograph of the Review of Osteoporosis and Mineral Metabolism[1] we included a table in which we presented the annual cost of the different drugs approved in Spain for the treatment of postmenopausal osteoporosis.
Subsequently, on the 30th December 2011, a resolution was published in the BOE due to which the reference prices of medicines were reviewed[2], modifying downwards the prices of all drugs.
For this reason, we have reviewed and updated the aforementioned table, including generic ibandronate, which was not available at the time of publication (Table1).
The prices are shown with or without VAT, depending on whether they apply to the Spanish peninsular or to the Canary Islands, where VAT is not applied. The Canary Islands indirect tax "Impuesto General Indirecto Canario" (IGIC) is not applied to pharmaceutical drugs, which means that the final price is net of VAT. Pharmaceutical drugs, which are packaged as 28 pills, are calculated at 13 packets per year, since it needs to be taken into account that pills in packets of 28 provide 28 x 12 months = 336 pills each year, with 29 more pills (1 packet) required. In drugs which are presented as weekly pills it is necessary to make the same correction (4 weeks x 12 months = 48 weeks, the year being 52 weeks), which also means that an additional packet needs to be added to correct the calculation of the annual cost. The same happens with nasal calcitonin. The exceptions, in the case of drugs administered orally, are monthly ibandronate and risedronate, whose calculation, due to their monthly administration, is made over 12 months. In the case of denosumab, its weekly administration is subcutaneous and comes with a preloaded syringe and needle. Finally, in the case of zoledronic acid it is necessary to add the price of the 5 ml vial, the cost of 1 syringe, needle and 100 ml of saline solution, plus the cost of the staff at the day hospital or place where it is administered, which varies from one hospital to another.

Table 1 on page 44

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Table 1. Annual cost of different drugs approved in Spain for the treatment of postmenopausal osteoporosis

Active	Trade name	Dose. Period. Way	Presentation	Cost package (with VAT)	Annual cost (with VAT)	Cost package (no VAT)	Annual cost (No/VAT)
Zoledronic acid	Aclasta	5 mg. Annual. I.V	Bottle 100 ml	422.65 €	422.65 €	406.39 €	406.39 €
Alendronate	Fosamax	70 mg. Weekly. Oral	Tablets x 4	14.71 €	191.23 €	14.14 €	183.82 €
Alendronate	Generic	70 mg. Weekly. Oral	Tablets x 4	14.71 €	191.23 €	14.14 €	183.82 €
Alendronate + Vit D	Fosavance. Adrovance	70 mg. Weekly. Oral	Tablets x 4	28.01 €	364.13 €	26.95 €	350.35 €
Weekly risedronate	Acrel, Actonel	35 mg. Weekly. Oral	Tablets x 4	22.12 €	287.56 €	21.25 €	276.25 €
Weekly risedronate	Generic	35 mg. Weekly. Oral	Tablets x 4	22.12 €	287.56 €	21.25 €	276.25 €
Weekly risedronate	Acrel, Actonel	75 mg. Monthly 2 days. Oral	Tablets x 2	24.57 €	294.84 €	23.63 €	283.56 €
Ibandronate	Bonviva. Bondenza	150 mg. Monthly. Oral	Tablets x 1	20.79 €	249.48 €	19.99 €	239.88 €
Ibandronate	Generic	150 mg. Monthly. Oral	Tablets x 1	20,79 €	249,48 €	19,99 €	239,88 €
Strontium ranelate	Protelos. Osseor	2 g. Daily. Oral	Envelopes x 28	49.39 €	642.07 €	47.49 €	617.37 €
PTH 1-34	Forsteo	20 mcg. Daily. Subcutaneous	Pre-filled pen X 28	405.38 €	5,269.94 €	389.79 €	5,067.27 €
PTH 1-84	Preotact	100 mcg. Daily. Subcutaneous	2 Cartridges x 14	396.19 €	5,150.47 €	380.95 €	4,952.35 €
Raloxifene	Evista. Optruma	60 mg. Daily. Oral	Tablets x 28	20.64 €	268.32 €	19.85 €	258.05 €
Raloxifene	Generic	60 mg. Daily. Oral	Tablets x 28	20,64 €	268,32 €	19,85 €	258,05 €
Bazedoxifene	Conbriza	20 mg. Daily. Oral	Tablets x 28	34.41 €	447.33 €	33.36 €	433.68 €
Denosumab	Prolia	60 mg. Semiannua. Subcutaneous	Pre-filled syringe x 1	240.15 €	480.30 €	230.54 €	460.08 €
Calcitonin nasal	Miacalcic. Several	200 UI. Daily. Nasal	Nebulizer x 28	75.01 €	975.13 €	72.13 €	937.69 €