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Committee of experts

The debate over the FRAX scale

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Clinical judgement, empirical, intuitive and based on experience, is one of the pillars of clinical decision-making. Along with clinical tests ("evidence"), and at an equal level, it serves to adapt what science offers to the individual patient. Osteoporosis is no exception. For years, we clinicians have used a long list of clinical risk factors, some modifiable, others not, to evaluate in each patient how much risk we must counteract with our interventions in a typical cost-benefit analysis.

The problem is that the quantification of this risk has been difficult. Other fields of pathology have preceded us in the search for formulae which permit us to calculate the risk of an individual patient becoming ill, attributing its relative weight, if they have it, to each of the factors which play a role in the determining the risk. In the case of osteoporosis, the risk of fracture.

Numerous scales have come to be constructed with this intention in recent years. Scales such as ORAI, Fracture Index, etc., have enjoyed limited approval their use was complex, or because their predictive capacity was (or was seen to be) limited.

After a long gestation, the FRAX scale has been put at the clinicians' disposal.

Its immediate success remains certain because it has generated a fierce debate from the start. Other reasons explain the whys and wherefores of its impact. Based on a broad mega-analysis of prospective cohort studies, from a number of countries, it is more methodologically rigorous and internationally representative than any earlier studies have been. Endorsed by the OMS and with the prestige of its creators, it has been adapted to many countries and translated into their respective languages. In addition, it is clinically plausible since it introduces various elements demonstrated as key to the determination of risk of fracture, and allows the qualification of absolute risk at ten years in each case both for femoral fracture and for the principal fractures resulting from osteoporosis.

However, since the beginning there has been something lacking in the calculation of risk which it offers. Although it permits estimation independent of the measurement of bone density, its addition is important in order to refine the calculation. In this case, however, the measurement is limited to the femoral neck, often dissociated from more important deteriorations in other parts of the body, such as the spinal column, which is no less robust than the measurement of the whole femur. There are powerful independent predictors of risk which are not taken into account, such as, for example, the frequent occurrence of falls, or a diet highly deficient in calcium. The estimate of some factors is very approximate. Thus, having had one or a number of falls, having taken a very high or very low dose of corticoids, or the existence, or not, of some diseases strongly associated with osteoporosis, are all valued equally. What's more, its applicability remains limited to women not previously treated, excluding a great number of cases which we deal with daily. It is also certain that the epidemiological baseline for the incidence of fractures is approximate for the majority of the countries which have adapted the tool.

Two recent publications, based on the SOF (Study of Osteoporotic Fractures) and on the analysis of the placebo group of the pivotal study of alendronate (the FIT study), have started to open a crack in its credibility. Both studies have confirmed that the predictive capacity of using simply age + BMD or age + previous fracture[1] in one study, or age + BMD + vertebral fracture[2] in the other is equally correct as using the FRAX scale.

In Spain these limitations have similarly been detected by means of an analysis of a wide prospective cohort study. As much for its for its over- as for its under-evaluation of risk, in cases of extreme risk of fracture observed, the linearity of the tool is limited[3].

What can we conclude? Above all we must congratulate those who have created the FRAX scale. Without a doubt it is a crucial advance in our clinical analysis of osteoporosis. Imperfect, of limited validity, with methodological defects, with telling shortcomings. And yet it represents the first global scale, which will mark a new paradigm in tackling osteoporosis, since it will be, without a doubt, the vertebral column on which we are going to work in the coming years. To perfect and

improve it in its applicability to specific countries is going to be the immediate task in its development. In the meantime, its judicious use, conscious of its limitations, will be a help in our clinical practice. As always, returning to clinical judgement.

Jesús Hurtado

It is inevitable that we dedicate some words to the memory of Jesús. No-one who knew him can dispute his qualities. A terribly human person, discreet, a hard worker, straightforward, affectionate, far-sighted, a scientific sage and doctor…All these descriptions, which are routinely applied to those who have died, most of the time simply because they are dead, are strongly applicable to Jesús. Exemplary in his life and in his passing towards death, he was a point of reference for all those who knew, and also, loved him. For his immutable smile and for the peace he radiated. Let us all enjoy his memory.

Bibliography

1. Ensrud KE, Lui LY, Taylor BC, Schousboe JT, Donaldson MG, Fink HA, et al. Study of Osteoporotic Fractures Research Group. A comparison of prediction models for fractures in older women: is more better? Arch Intern Med 2009;169:2087-94.
2. Donaldson MG, Palermo L, Schousboe JT, Ensrud KE, Hochberg MC, Cummings SR. FRAX and risk of vertebral fractures: the fracture intervention trial. J Bone Miner Res 2009;24:1793-9.
3. González-Macías J, Vila J, Marín F, Díez-Pérez A. Analysis of the predictive performance of the FRAX® tool in a cohort of 5201 women in the ECOSAP study. 14 Congress of SEIOMM. Santander 27-30 October 2009.

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On behalf of the working group on osteoporosis of the Spanish Society of Internal Medicine
(See Annex 1)

The prevalence of vertebral fractures in patients attending Internal Medicine outpatient clinics

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Summary

Background: Fractures are a clinical complication of osteoporosis, and among them vertebral fractures (VF) are the most frequent. This type of fracture is often asymptomatic or happens unnoticed and is not diagnosed.

Objective: To study the prevalence of previously non-diagnosed vertebral fractures in a population of post menopausal women over 50, who have attended an Internal Medicine outpatient clinic because of chronic back pain.

Material and methods: 273 women participated in the study, which comprised a group of cases (Group I) and a control group (Group II). Group I consisted of 202 post-menopausal women who had chronic back pain at the time they attended one of 13 Internal Medicine outpatient clinics across Spain. Group II was made up of 71 women who did not have back pain, and who were used as controls. To register any risk factors for osteoporosis, and any clinical symptoms, a questionnaire, previously validated and used in other similar clinical studies by SEIOMM members, was completed for all the female patients. A lateral thoracic and lumbar X-ray was also carried out on all female patients. The interpretation of the X-rays was done centrally. The Genant criteria for vertebral deformity were used for the diagnosis of the vertebral fractures.

Results: The post-menopausal women with chronic back pain were shorter in height than those who did not have back pain (154 ± 7.7 cm compared with 157 ± 7.7 cm, p= 0.005), they had a greater prevalence of kyphosis (54% vs 32.4%) and a higher prevalence of VF (15.8% vs 2.8%, p= 0.004). No statistically significant differences in the prevalence of fractures in total, hip fractures, Colles fractures and other fractures, were found between the two groups. BMI, VFs and kyphosis showed an independent and statistically significant association with back pain.

Conclusions: At the time of the study 15.8% of post-menopausal women with chronic back pain presented with at least one VF. In addition, they had a higher prevalence of kyphosis, and were on average 3cm shorter, than the women without back pain. Given that these fractures were not previously diagnosed, we suggest carrying out a lateral thoracic-lumbar X-ray on these patients, in order to establish a diagnosis and to start treatment as soon as possible.

Key words: *Vertebral fracture, Osteoporosis, Prevalence, Back pain.*

Introduction

Osteoporosis is a very common disease which predominantly affects older women, although it can affect both sexes[1,2]. It is estimated that from the age of 50 white women have a risk of osteoporotic fracture of almost 50% for the rest of their lives[3].

Fractures are a clinical complication of osteoporosis[4] and among them vertebral fractures (VF) are notable for their frequency, while notable for their seriousness are fractures of the proximal extremity of the femur – or fracture of the hip[3,5].

VFs, being the osteoporotic fracture most prevalent, often occur unnoticed and are not diagnosed. This is because on the one hand diagnosis requires a lateral X-ray of the spinal column, with the application of criteria for vertebral deformity which often don't coincide[6,7], while on other hand VFs can be asymptomatic[8]. In addition, back pain, which can be a symptom of VF, is often attributed to other diseases, or even to age.

Because of this we have carried out this study in a population of women who attended an Internal Medicine clinic suffering from chronic back pain, with the objective of studying in these patients the prevalence of undiagnosed VF.

Material and methods

This work is a prospective study, with cases and controls, in which the cases were post-menopausal women over 50 who attended an Internal Medicine outpatient clinic, presenting with chronic back pain. The following criteria for including patients in the study were used: a) having back pain, located in the dorsal and/or lumbar spinal column; b) that the pain was present for at least 3 months and; c) that there was no already-known cause for the pain. Back pain located in the dorsal and lumbar spinal column was included, while pain in the cervical spinal column was excluded. The control group was made up of women of the same age with no back pain, friends, but without family connections, invited by the patients themselves, not having had dorsal or lumbar back pain for at least 6 months before the consultation, and not having taken any treatment for this condition during the same period of time.

The patients were informed of the objectives of the study and their consent requested. For all subjects a questionnaire, previously validated and used in other similar clinical studies[9-11], was completed to gather clinical data on osteoporosis. A basic physical examination was also conducted, including measurement of height and weight in light clothing. Lastly, a lateral thoracic-lumbar X-ray was carried out on the subjects. All the X-rays were brought together and studied by two radiologists (PA and RFP, see Annex 1). In cases of discrepancy an assessment was requested from a specialist in bone mineral metabolism (MSH). For the diagnosis of VF the Genant criteria[12], were used. The study was carried out with approval of the Committee on Medical Trials of the Island University Hospital of Gran Canaria.

The data collected were entered into a database already set up in the statistical programme SPSS (Statistical Package for the Social Sciences), for which we had the necessary legal licences. For the analysis of the data the Kolmogorov-Smirnoff test was applied to establish the goodness of fit to normality for the variables studied. For each group studied, the variables categorised were summarised in frequencies and percentages and the numericals in averages and standard deviations. The percentages were compared using the chi–square test and the averages using the t-test. Those variables which showed a significant association with the final objective (endpoint) were subjected to a multidimensional logistic analysis. A retrospective selection of variables based on the test of ratio of verisimilitude was carried out. The association of each variable selected with the final objective was expressed through the p-value deduced from the final logistical model and the *odd-ratio*, which was estimated with a confidence interval (CI) of 95%. A contrast of hypothesis was considered significant when the corresponding p-value was less than 0.05.

Results

A total of 273 post-menopausal women, 202 cases and 71 controls participated in the study, recruited by a total of 13 working groups across Spain. In Table 1 the basal characteristics of the population studied are shown. The average age of the participants was in the region of 70 years (69.7 ± 11.0 years in the cases and 71.3 ± 11.3 years in the controls) with no statistically significant difference between the two groups. Neither was their any difference in the weight (66.3 ± 14.0 Kg as opposed to 65.5 ± 12.6 Kg, p= 0.687) nor in the body mass index (28.0 ± 5.5 Kg/m^2 as opposed to 26.7 ± 4.8 Kg/m^2, p= 0.081). The women who had back pain were shorter in height than the controls (154 ± 7.7 cm as opposed to 157 ± 7.7 cm, p= 0.005).

Table 2 shows the prevalence of other concomitant diseases and lifestyle determinants in both groups in the study. One can see that more than half (54%) of those women who have back pain also have kyphosis, a sign which is seen in less than a third of the women who do not have back pain (32.4%), p= 0.002. The distribution of the other diseases - diabetes, chronic renal failure, obesity and dyslipidemia – as well as some lifestyle and risk factors – alcohol consumption and family history of osteoporotic fractures – were similar in both groups.

In Table 3 we observe the distribution of fractures in both groups. 15.8% of post-menopausal women with back pain have, at least one VF, whilst in the control group we see that the prevalence is 2.8%, p= 0.004. The distribution of other fractures was similar in both groups: all fractures, Colles fracture, hip fracture and other fractures.

Finally, a multidimensional logistic analysis was carried out to discover which factors show an independent association with back pain. The results of this analysis, set out in Table 4, show these factors as being the body mass index, the existence of VFs and Kyphosis, with VFs being the variable which shows the strongest independent association (OR 6.325, CI: 1.450; 27.6, p= 0.014).

Discussion

Fractures due to fragility constitute the principal clinical complication of osteoporosis, and among these VF has a special importance. A broad epidemiological study carried out in Europe demonstrated that between 20% and 25% of the population over 50 of both sexes have a VF[13], which often occurs unnoticed, since it is the only fracture in which there is neither a line of fracture nor a break in continuity between the extremes. VF can consist of a deformity, or crushing, of its morphology, requiring for its correct diagnosis, in addition to a lateral thoracic-dorsal X-ray, the application of what are known as criteria of vertebral deformity[6], of which there are many, few of which coincide[7,12]. This was observed in EVOS study, which found almost double the prevalence of VF whether they applied the deformity criteria of Eastell or McCloskey[13]. Another factor which leads to VFs being underestimated is the fact that they are sometimes asymptomatic, or are experienced as short term back pain[4,14].

VF is in itself a risk factor in suffering a new fracture, be it vertebral or hip[15,16]. A study has been published which states that 20% of women with VF without treatment suffer a new VF within a year[17], without forgetting that VF, as with the remaining osteoporotic fractures, carries a higher morbidity[5] and leads to an increase in mortality[18,19]. Hence the importance recognising this.

Our study was carried out with a population of patients who attended an Internal Medicine outpatient clinic because of back pain, or in whom this was confirmed when their clinical history was taken, this not having been the explicit reason for their attendance at the clinic. Our aim was to make a first attempt at understanding the prevalence of VF in these ambulatory patients, a study motivated by the results we obtained from other work carried out by the working group on osteoporosis of SEMI, in which we found a higher prevalence of VF, 62.6%, in those patients who were admitted and treated for a hip fracture[11]. Although in this population of high risk for osteoporosis this result was no surprise, it was surprising that in the control group in this study, who were chosen from among patients admitted to the Internal Medicine wards for other processes unrelated to OP and without apparent high risk of osteoporosis, showed a prevalence of VF of 50%. In the current study 15.8% of postmenopausal women with back pain have at least one VF, whilst in the control group this prevalence was only 2.8%. Previously, another co-operative European study confirmed that up to 25% of postmenopausal women have at least one VF[12], however, the same study clearly stated that many of these fractures were asymptomatic. However, all the patients in our study should be considered as having symptomatic fractures since they attended precisely for back pain. We do not know the reasons why the prevalence of vertebral fractures in the control group was so low.

We did not find statistically significant differences in the distribution of other diseases such as diabetes, obesity, chronic renal failure and dyslipidemia, or in the distribution of some lifestyle and risk factors such as tobacco and alcohol consumption, or family history of osteoporotic fractures. As was expected, women with VF had a higher prevalence of kyphosis than the controls. On the other hand we did not find any statistically significant differences in other fragility-related fractures, neither in general, nor independently in hip fractures, Colles fractures or other fractures, including fractures of humerus, tibia and ribs.

By carrying out a multidimentional logistic analysis we found an independent association between back pain and the variables BMI, VF and kyphosis. We interpreted these results as being interrelated. We

Table 1. Basal characteristics of the population studied

	Back pain		
	Yes N = 202	**No N= 71**	**Value of p**
Age (years)	69.7 ± 11.0	71.3 ± 11.3	0.294
Weight (kg)	66.3 ± 14.0	65.5 ± 12.6	0.687
Height (cm)	154 ± 7.7	157 ± 7.7	0.005
BMI (kg/m^2)	28.0 ± 5.5	26.7 ± 4.8	0.081

Body Mass Index (BMI): Weight (kg)/height^2 (cm)

Table 2. Prevalence of concomitant diseases in the groups of the study

	Cases Number (%)	**Controls Number (%)**	**Value of p**
Number	202 (100)	71 (100)	
Diabetes	37 (18.3)	18 (25.7)	0.184
Obesity	65 (32.3)	16 (22.9)	0.136
Chronic renal failure	19 (9.9)	4 (6.1)	0.340
Tobacco	13 (6.4)	6 (8.5)	0.566
Alcohol	6 (3.0)	3 (4.3)	0.601
Dyslipidemia	76 (38.4)	27 (39.7)	0.847
Family history of osteoporotic fractures	44 (22.0)	16 (20.6)	0.807
Kyphosis	107 (54.0)	22 (32.4)	0.002

Table 3. Prevalence of fractures by group studied

	Cases Number (%)	Controls Number (%)	Value of p
Presence of any fracture	90 (44.6)	28 (39.4)	0.454
Vertebral fracture	32 (15.8)	2 (2.8)	0.004
Hip fracture	16 (7.9)	11 (15.5)	0.066
Colles fracture	20 (9.9)	10 (14.1)	0.332
Other fractures	32 (15.8)	12 (16.9)	0.835

Table 4. Multidimensional logistic analysis: factors having an independent association with back pain

Factor	Value of p	*Odd Ratio* (CI – 95%)
BMI (Por Kg/m^2)	0.030	1.066 (1.005 ; 1.130)
Vertebral fractures	0.014	6.325 (1.450 ; 27.6)
Kyphosis	0.008	2.246 (1.237 ; 4.077)

believe that the higher the BMI, the greater back pain is observed in patients who already have at least one VF, which in turn influences the development of kyphosis.

In conclusion, VF is found in 15.8% of postmenopausal women who have back pain, as well as a higher prevalence of kyphosis. Given that up to 20% of women who have a VF and have not had treatment suffer a new VF within one year[16], it is advisable to take into account this fact with a view to indicating the most appropriate therapeutic measures at the time.

Bibliography

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, March 7-29, 2000: highlights of the conference. South Med J 2001;94:569-73.
2. Melton LJ, 3rd. The prevalence of osteoporosis: gender and racial comparison. Calcif Tissue Int 2001;69:179-81.
3. Melton LJ, 3rd. Who has osteoporosis? A conflict between clinical and public health perspectives. J Bone Miner Res 2000;15:2309-14.
4. Becker C. Pathophysiology and clinical manifestations of osteoporosis. Clin Cornerstone 2006;8:19-27.
5. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359:1761-7.
6. Grados F, Roux C, de Vernejoul MC, Utard G, Sebert JL, Fardellone P. Comparison of four morphometric definitions and a semiquantitative consensus reading for assessing prevalent vertebral fractures. Osteoporos Int 2001;12:716-22.
7. Gómez de Tejada Romero MJ, Sosa Henríquez M. ¿Qué queremos decir exactamente con "fracturas no vertebrales"? (O ¿por qué no llamar a las cosas por su nombre?). Rev Esp Enf Metabol Oseas 2005;14:39-40.
8. Wark JD. Osteoporosis: a global perspective. Bulletin of the World Health Organization 1999;77:424-6.
9. Sosa M, Saavedra P, del Pino-Montes J, Alegre J, Perez-Cano R, Guerra GM, et al. Postmenopausal women with colles' fracture have lower values of bone mineral density than controls as measured by Quantitative Ultrasound and densitometry. J Clin Densitom 2005;8:430-5.
10. Sosa M, Saavedra P, Valero C, Guanabens N, Nogues X, del Pino-Montes J et al. Inhaled steroids do not decrease bone mineral density but increase risk of fractures: data from the GIUMO Study Group. J Clin Densitom 2006;9:154-8.
11 Sosa M, Saavedra P en nombre del grupo de trabajo en osteoporosis de la Sociedad Española de Medicina Interna (SEMI). Prevalencia de fracturas vertebrales en pacientes con fractura de cadera. Rev Clin Esp 2007;207:464-8.
12 Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
13. Cooper C, O'Neill T, Silman A. The epidemiology of vertebral fractures. European Vertebral Osteoporosis Study Group. Bone 1993;14 Suppl 1:S89-97.
14. Ferrar L, Jiang G, Armbrecht G, Reid DM, Roux C, Gluer CC et al. Is short vertebral height always an osteoporotic fracture? The Osteoporosis and Ultrasound Study (OPUS). Bone 2007;41:5-12.
15. Melton LJ, 3rd, Atkinson EJ, Cooper C, O'Fallon WM, Riggs BL. Vertebral fractures predict subsequent fractures. Osteoporos Int 1999;10:214-21.
16. Kanis JA, Johnell O, De Laet C, Johansson H, Oden A, Delmas P, et al. A meta-analysis of previous fracture and subsequent fracture risk. Bone 2004;35:375-82.
17. Lindsay R, Silverman SL, Cooper C, Hanley DA, Barton I, Broy SB, et al. Risk of new vertebral fracture in the year following a fracture. JAMA 2001;285:320-3.
18. Melton LJ, 3rd. Excess mortality following vertebral fracture. J Am Geriatrics Soc 2000;48:338-9.
19. Bliuc D, Nguyen ND, Milch VE, Nguyen TV, Eisman JA, Center JR. Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women. JAMA 2009;301:513-21.

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Prevalence of osteoporosis in patients with acute coronary syndrome

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Summary

Objectives: To assess the relationship between osteoporosis and acute coronary syndrome.
Material and Methods: This study involved 163 patients aged between 39 and 79 years, with an average age of 62 years. Of these, 83 were patients with acute coronary syndrome (90% acute myocardial infarction; 10% unstable angina). The other 80 patients belonged to a control group without cardiovascular disease.
Anthropometric measures were taken and densitometry carried out in both the lumbar spinal column and femoral neck. We considered a T-score < -2.5 DE as osteoporosis.
Results: No statistically significant differences were found regarding bone mineral density between the group of cases and the control group. Stratifying the data by osteoporotic disease, we observed that the prevalence is greater, to a statistically significant extent, in the group of patients with acute coronary syndrome. In analysing the data by sex, a greater prevalence of osteoporosis was found only in the group of women with acute coronary syndrome, the same relationship was not found in the group of men.
Conclusions: In our study we observed a greater prevalence of osteoporosis in patients with acute coronary syndrome.

Key words: *Osteoporosis, Bone mineral density, Acute coronary syndrome.*

Introduction

Atherosclerosi and osteoporosis are chronic degenerative diseases with a high incidence in the general population, representing two important health problems whose prevalence will increase with the average age of the population[5,2]. They are silent processes with high economic cost which are manifested through their complications, acute vascular accidents and osteoporotic fractures. Various epidemiological studies have shown an independent association of both processes with age[3,4].

Atherosclerosis, which appears in coronary disease, cerebro-vascular disease and peripheral arterial disease, is responsible for the majority of cardiovascular diseases. It is characterised by a chronic arterial inflammation caused, and exacerbated by disorders in the metabolism of lipids and other clearly identified risk factors[5]. A characteristic phenomenon of atherosclerosis is the calcification which is set in motion by an active process in which inflammatory cytokines and other mediators which regulate the phosphocalcic metabolism are involved[6]. These mechanisms can intervene in an opposing phenomenon which is, at the level of bone, characterised by a decrease in bone mineral content and changes in the micro-architecture which define osteoporosis. What is notable is the association of the two processes, which share mechanisms, but which have a different expression.

There are numerous studies which evaluate the relationship between cardiovascular diseases and osteoporosis. There are two different types of study, transversal and longitudinal, the latter being of greater interest. These studies usually use substitute markers to assess the association of the two processes, vascular calcification in atherosclerosis and bone mineral density in osteoporosis. Of greater value are those studies which use the presence of cardiovascular disease and fractures as makers for disease. Magnus et al.[7] using the NHANES III database found an independent and statistically significant relationship between previous myocardial infarction and low bone mass. The effect was observed only in men and was independent of age, race, alcohol consumption, physical exercise and body mass index. Also, in patients with cardiac failure of functional class II/III a lower bone mass, adjusted for age and sex, was found, compared to the control group[8]. Farhat et al.[9] observed that the volumetric BMD in the lumbar spinal column was decreased in individuals with cardiovascular disease, the effect being independent of age or of levels of inflammatory cytokines, IL-1 and IL-6. This aspect has not been analysed in the Spanish population. The objective of this study is to assess the prevalence of osteoporosis in patients with acute coronary syndrome in our environment.

Material and methods

A case-controlled transversal study was carried out in the western health area of Valladolid. During the period 2001-2003 163 patients were analysed, 83 hospitalised by acute myocardial infarction and unstable angina, and 80 controls. Criteria for exclusion were the presence of alcoholism, neoplasia, hyper- or hypocalcemia and receipt of drug treatments which modify bone metabolism. In addition, in order to gather anthropometric data, densitometry was carried out on all patients in the four weeks prior to their inclusion. The control group was made up of individuals of the same age and sex without ischaemic cardiopathy. The densitometry was carried out in the lumbar spinal column (L2-L4) and femoral neck using a double photon densitometer (DXA, Lunar Corporation, Madison, Wisconsin, USA). The BMD (Bone Mineral Density) was expressed in g/m^2 and determined the T-score, according to the reference values provided by the manufacturer of the densitometer. Patients with a T-score < -2.5 were considered to be osteoporotic.

The results are expressed as an average ± standard deviation. The comparison of averages was carried out through a student's t test and the qualitative variables were compared using a chi-square test. The correlation between variables was found using Pearson's r. The statistical programme used was SPSS (SPSS, Chicago, Ill; Base 11.4 for Windows).

Results

163 patients were studied, of which 83 had acute coronary syndrome and 80 were controls. The average age of the patients (61 ± 10 years) was less than that of the controls (64 ± 8 years) with those individuals with acute coronary syndrome being predominantly males. The characteristics of the cases and the controls are seen in Table 1.

There were no differences in the bone mineral density in the lumbar spinal column (1.136 ± 0.22 g/cm^2 vs 1.122 ± 0.16 g/cm^2, p= 0.457) and femoral neck (0.920 ± 0.15 g/cm^2 vs 0.933 ± 0.12 g/cm^2 p= 0.882). 31% of those patients with acute coronary syndrome were osteoporotic as against 14% in the control group, the difference being statistically significant, p= 0.017. In analysing by sex, in the women the difference remained significant (48% vs 17%, p= 0.007) while in the men it did not (21% vs 7%, p= 0.183) (Figures 1 and 2). There were 15 women with osteoporosis in the patients with acute coronary syndrome as opposed to 9 women in the control group. In the men, 11 patients presented with osteoporosis as opposed to 2 in the control group.

Discussion

The results of our study show that the patients with acute coronary syndrome had a greater prevalence of osteoporosis than in the control population, although only in the group of women is this statistically significant. Our results show some differences in relation to NHANES III. This study found a lower bone mass in the population with myocardial infarction and specifically in men. In our study we did not find differences in bone

mass, although there were differences in the prevalence of osteoporosis, specifically in women. Our female patients were all postmenopausal, for which reason they probably had common factors which acted on both diseases. These could be genetic, vascular risk factors which exert a prejudicial effect on bone mass or physiopathological mechanisms shared by both entities.

Table 1. Characteristics of the case-controls

	Cases	Controls	
Age in years	61 ± 10	64 ± 8	0.044
Sex	31M, 52V	52M, 28V	
BDM L2-L4 g/cm^2	1.136 ± 0.22	1.122 ± 0.16	0.457
Femoral neck g/cm^2	0.920 ± 0.15	0.933 ± 0.12	0.882

Genetic factors play an important role in osteoporosis. Studies of twins and families have estimated that between 50% and 85% of bone mass is genetically determined[10]. Ateriothrombotic cardiovascular diseases are multifactorial diseases with a significant genetic component. In both diseases the number of genes which are involved is large, with a small contribution from each of them.

The metabolic pathway Wnt-LPR is key to the formation of bone[11]. Recently, a missense mutation in LPR6, which codes for a co-receptor, has been described in an Iranian family. Cysteine is substituted by arginine thus damaging the messaging of Wnt *in vitro*. These patients carry a major risk of coronary disease, of low bone mass and of osteoporotic fracture, suggesting that both diseased could be pleiotropic consequences of an alteration in the Wnt metabolic pathway[12].

The RANK/OPG system is the principal regulatory mechanism for bone resorption, polymorphisms which regulate osteoprotegerine (OPG) having been implicated in both processes[13]. Polymorphisms within the promoter of the OPG gene (A163G and T245G) are detected most frequently in patients with vertebral fracture[14],while other polymorphisms located in the promoter T950C and in exon 1, G1181C, are associated with a high risk of ischaemic cardiopathy, especially the combination of both polymorphisms[15].

Polymorphism in the codon 986 (A986S) of the calcium-sensing receptor (CASR) has been associated with elevated levels of calcium and an increase in the prevalence of osteoporosis[16,17]. The same polymorphism can be a predictor for ischaemic cardiopathy, myocardial infarction and cardiovascular mortality[18]. However, the relationship with osteoporosis appears only in the population of young people, but not in postmenopausal women, nor in people with hypertension[19,20]. The klotho gene is associated with age-related loss of bone mass both in postmenopausal women and in men[21]. In the Japanese population it has been observed that the allele A of the polymorphism G396A was more frequent in patients with ischaemic cardiopathy than in a control group, with an OR of 1.82 (p= 0.004)[22].

All these data indicate a possible role for genetic mechanisms in the association between osteoporosis and cardiopathy, although the contribution of each one of these polymorphisms might be small.

There are vascular risk factors which determine a high incidence of cardiovascular disease. These elements can have an influence on bone metabolism, reducing bone mass, facilitating the appearance of osteoporosis.

Tobacco is a risk factor for atherosclerosis. Its effects on bone metabolism have been little studied. In women it acts at the level of oestrogens, diminishing their levels and causing the loss of their protector role. In addition it produces a decrease in the blood levels of 25-hydoxivitamin D which is not accompanied by raised levels of paratohormone (PTH)[23]. These changes can provoke a decrease in BMD, which has been described predominantly in the lumbar region, of a dose-dependent form, although not all studies are in agreement on this.

The relationship between osteoporosis and hypertension is not clearly established, although numerous changes in the metabolism of calcium in patients with hypertension, which can cause a decrease in bone mass, have been described. Among these changes are included a decrease in ionic calcium, and an increase in calcuria and of urinary AMPc, raised levels of PTH and calcitriol and an increase in the intestinal absorption of calcium[24]. Of these only hypercalcuria has been associated with a decrease in bone mass. Most of the studies did not find a relationship between levels of arterial tension and bone mineral density[24]. In our population we found similar results, there being no greater risk of osteoporosis in the population with hypertension[25]. However, in a retrospective study which included 998 patients with hip fracture the presence of hypertension did increase the risk of fracture (1.49 OR, 95 % CI 1.3-1.8)[26].

Homocysteine is one of the new markers for vascular risk which is associated with an increased risk of osteoporotic fracture. Prospective studies carried out in European and American populations show that raised levels of homocysteine are associated with a greater risk of fracture[27,28]. However, not all studies obtain these results and those in which there has been an intervention to reduce blood levels of homocysteine have not seen a reduction in the number of fractures[29].

There are not many studies which relate plasmatic lipids, a substitute marker for atherosclerosis, with bone mineral density and/or osteoporot-

Figure 1. Women with osteoporosis

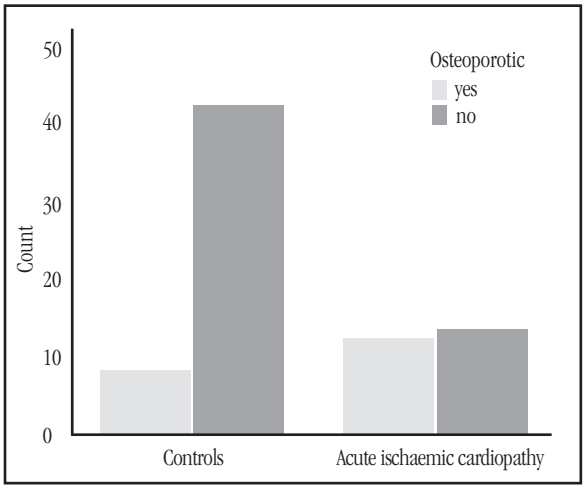
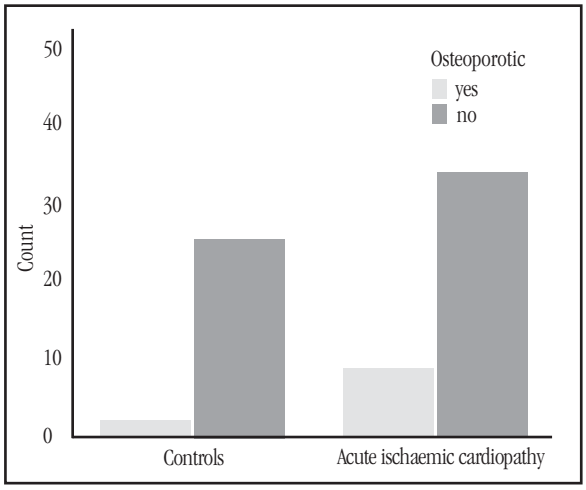


Figure 2. Men with osteoporosis



ic fracture. Broulik et al.[30] showed that osteoporotic women had higher levels of cholesterol than the controls. Yamaguchi et al.[31] found that LDL cholesterol was negatively related to BMD while HDL cholesterol was positively related. It was observed that those patients with low bone mass had higher concentrations of plasmatic lipids with a greater severity of vascular disease. In asian population similar data have been obtained[32]. Other studies have brought different results. The Framingham Osteoporosis Study did not show an association between cholesterol levels and the later appearance of osteoporosis[33]. Nor did Tanko et al.[34] find such a relationship in a study carried out in 340 postmenopausal women under 76 years of age. On the other hand, the influence of plasmatic lipids on peripheral bone mineral density in the diabetic population has not been demonstrated[35].

Similarly to that which happens with genetic factors, vascular risk factors can contribute to an increase in bone mass which appears in acute ischaemic cardiopathy, although not all studies are consistent on this. Recently there has been an attempt to evaluate the effect of a number of these factors, grouped as metabolic syndrome, on bone mass and osteoporotic fractures. The presence of metabolic syndrome is associated with higher bone mass but a greater risk of fractures[36].

Inflammation plays a central role in the appearance of atherosclerosis and its later development. Cells of the immune system are found in the initial phases of arteriosclerotic lesions, atheroma, and accelerate their later progression. The T lymphocytes are always present in the atherosclerotic lesions, predominantly the CD4 lymphocytes. These are capable of recognising antigens and differentiating (themselves from) type 1 helper cells (TH1). In their turn, the cytokines released by macrophages facilitate differentiation towards these cells. The TH1 cells go on to release specific cytokines, γ-interferon, interleukin-1 and tumour necrosis factor-alpha[37]. In osteoporosis the activity of the osteoclasts can be modulated by the action of gamma interferon (INF-γ) acting on necrosis factor-receptor-associated factor 6 (TRAF-6)[38]. The same mechanisms which intervene in the stimulation of bone resorption and facilitate the decrease in bone mineral density also facilitate the progression of the atheromatous plaques.

The most frequently occurring osteoporosis is postmenopausal osteoporosis which is initiated by a fall in oestrogens. Their reduction then provokes a disequilibrium in the TH1/TH2 relationship with the predominance of TH1, in a similar way as that described in atherosclerosis[39]. This is produced by an increase in local levels of IL-7 which then provoke an increase in concentrations of inflammatory cytokines, of RANKL and a decrease in TGF-β. This cytokine exerts a beneficial effect on the bone since it produces an increase in osteoblast activity and a decrease in their apoptosis[38]. There are numerous similarities in the local mechanisms, of an inflammatory nature, which intervene in osteoporosis and in atherosclerosis. These mechanisms were evaluated by Farhat et al.[9] in a broad study of patients with cardiovascular disease in which the effect of inflammatory cytokines (IL-6 and TNF-α) on bone mineral density were assessed. The patients presented higher levels of cytokines than the controls, but this bore no relationship to bone mineral density measured in a number of places. It should be taken into account that systemic levels of cytokines may not reflect that which occurs locally.

In conclusion, we can say that patients with acute coronary syndrome constitute a risk population for the appearance of osteoporosis, there being mechanisms which help us to explain this association.

Bibliography

1. Kado DM, Browner WS, Blackwell T, Gore R, Cummings SR. Rates of bone loos is associated with mortality in older women: aprospective study. J Bone Miner Res 2000;15:1974-80.
2. Bauer DC, Palermo L, Black D, Cauley JA. Quantitaive ultrasound and mortality: a prospective study. Osteoporosis Int 2002;13:606-12.
3. Hofbauer LC, Brueck CC, Shanahan CM, Schopper M, Dobnig H. Vascular calcification and osteoporosis, from clinical observation towards molecular understanding. Osteoporosis Int 2007;18:251-9.
4. Bagger YZ, Rasmunssen HB, Alexandersen P, Werge T, Christiansen C, Tankó LB. Links between cardiovascular disease and osteoporosis in postmenopausal women: serum lipids or atherosclerosis per se?. Osteoporosis Int 2007;18:505-12.
5. Hansson GK. Inflammation, atherosclerosis and coronary artery disease. N Engl J Med 2005;352:1685-95.
6. Doherty TM, Fitzpatrick LA, Inoue D, Quiao JH, Fishbein MC, Detrano RC, et al. Molecular, endocrine and genetic mechanisms of arterial calcification. Endocr Rev 2004;25:629-72.
7. Magnus JH, Broussard DL. Relationship between bone mineral density and myocardial infarction in US adults. Osteoporos Int 2005;16:2053-62.
8. Kenny AM, Boxer R, Walsh S, Hager WD, Raisz LG. Femoral bone mineral density in patients with heart failure. Osteoporos Int 2006;17:1420-7.
9. Farhat GN, Newman AB, Sutton-Tyrrell K, Matthews KA, Boudreau R, Schwartz AV, et al. The association of bone mineral density measures with incident cardiovascular disease in older adults. Osteoporos Int 2007;18:999-1008.
10. Livshits G. Quantitative genetics of circulating molecules associated with bone metabolism: A review. J Musculoskelet Neuronal Interact 2006;6:47-61.
11. Zaidi M. Skeletal remodeling in health and disease. Nat Med 2007;13:792-801.
12. Mani A, Radhakrishnan J, Wang HE, Mani A, Mani M, Nelson-Williams C, et al. LPR6 mutation in a family with early coronary disease and metabolic risk factors. Science 2007;315:1278-82.
13. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. J Clin Invest 2005;115:3318-25.
14. Langdahl BL, Carstens M, Stenkjaer L, Eriksen EF. Polymorphisms in the osteoprotegerin gene are assiated with osteoporotic fractures. J Bone Miner Res 2002;17:1744-51.
15. Soufi M, Schoppet M, Sattler AM, Herzum M, Maisch B, Hofbauer LC, et al. Osteoprotegerin gene polymorphisms in men with coronary artery disease. J Clin Endocrinol Metab 2004;89:3764-8.
16. Lorentzon M, Lorentzon R, Lerner UH, Nordström P. Calcium sensing receptor gene polymorhism, circulating calcium concentrations and bone mineral density in healthy adolescent girls. Eur J Endocrinol 2001; 144:257-61.
17. Brown EM, Hebert SC. Calcium-receptor-regulated parathyroid and renal function. Bone 1997;20:303-9.
18. März W, Seelhorst U, Wellnitz B, Tiran B, Obermayer-Pietsch B, Boehm BO, et al. Alanine to serine polymorphism at position 986 of the calcium-sensing receptor associated with coronary heart disease, myocardial infarction, all-cause, and cardiovascular mortality. J Clin Endocrinol Metab 2007;92:2363-9.
19. Cetani F, Pardi E, Borsari S, Vignali E, Dipollina G, Berge V, et al. Calcium-sensing receptor gene polymorhism is not associated with bone mineral density in italian postmenopausal women. Eur J Endocrinol 2003:148:603-7.
20. Perez-Castrillon JL, Sanz A, Silva J, Justo I, Velasco E, Dueñas A. Calcium-sensing receptor gene A986S polymorphism and bone mass in hypertensive women. Arch Med Res 2006;37:607-11.
21. Zarrabeitia MT, Hernandez JL, Valero C, Zarrabeitia AL, Ortiz F, Gonzalez–Macias J, et al. Klotho gene polymorphism and male bone mass. Calcif Tissue Int 2007;80:10-4.
22. Imamura A, Okumura K, Ogawa Y, Murakami R, Torigoe M, Numaguchi Y, et al. Khloto gene polymorphism may be a genetic risk factor for atherosclerotic coronary artery disease but not for vasospastic angina in Japanese. Clin Chim Acta 2006;371:66-70.
23. Supervía A, Nogues X, Enjuanes A, Villa J, Mellibovsky L, Serrano S, et al. Effect of smoking and smoking cessation on bone mass, bone remodeling, vitamin D, PTH and sex hormones. J Musculoskelet Neuronal Interact 2006;6:234-41.
24. Perez-Castrillon JL, Justo I, Sanz-Cantalapiedra A, Pueyo C, Hernandez G, Dueñas A. Effect of the Antihypertensive Treatment on the Bone Mineral Density and Osteoporotic Fracture. Current Hypert Rev 2005;1:61-6.
25. Perez-Castrillon JL, Justo I, Silva J, Sanz A, Martin-Escudero JC, Igea R, et al. Relationship between bone mineral density and angiotensin converting enzyme polymorphism in hypertensive postmenopausal women. Am J Hypertens 2003;16:233-5.
26. Pérez-Castrillón JL, Martín-Escudero JC, Alvarez-Manzanares P, Cortes Sancho R, Iglesias Zamora S, García Alonso M. Hypertension as a risk factor for hip fracture. Am J Hypertens 2005;18:146-7.
27. Van Meurs JB, Dhonukshe-Rutten RA, Pluijm SM, Van der Klift M, De Jonge R, Lindemans J, et al. Homocysteine levels and the risk of osteoporotic fracture. N Engl J Med 2004;350:2033-41.
28. McLean RR, Jacques PF, Selhub J, Tucker KL, Samelson EJ, Broe KE, et al. Homocysteine as a predictive factor for hip fracturew in older persons. N Engl J Med 2004;350:2033-41.
29. Sawka AM, Ray JG, Yi Q, Josse RG, Lonn E. Randomized clinical trial of homocysteine level-lowering therapy and fractures. Arch Intern Med 2007;167:2136-9.
30. Broulik PD, Kapitola J. Interelations between body weight, cigarette smoking and spine mineral density in osteoporotic Czech women. Endocr Regul 1993;27:57-60.
31. Yamaguchi T, Sugimoto T, Yano S, Yamauchi M, Sowa H, Chen Q, et al. Plasma lipids and osteoporosis in postmenopausal women. Endocr J 2002;49:211-7.
32. Cui LH, Shin MH, Chung EK, Lee YH, Kweon SS, Park KS, et al. Association between bone mineral densities and serum lipid profiles of pre and post-menopausal rural women in South Korea. Osteoporos Int 2005;16:1975-81.
33. Samelson EJ, Cupples LA, Hannan MT, Wilson PWF, Williams SA, Vaccarino VZ, et al. Long-term effects of serum cholesterol on bone mineral density in women and men: The Framingham Osteoporosis Study. Bone 2004;34:557-61.
34. Tanko LB, Bagger YZ, Nielsen SB, Christiansen C. Does serum cholesterol contribute to vertebral bone loss in postmenopausal women? Bone 2003;32:8-14.
35. Pérez-Castrillón JL, De Luis D, Martín-Escudero JC, Asensio T, Del Amo R, Izaola I. Non-insulin-dependent diabetes, bone mineral density, and cardiovascular risk factors. J Diabetes Complications 2004;18:317-21.
36. Von Muhlen D, Safii S, Jassal SK, Svartberg J, Barret-Connor E. Associations between the metabolic syndrome and bone health in older men and women: the Rancho Bernardo Study. Osteoporos Int 2007;18:1334-7.
37. Kuiper J, Van Puijvelde G, Van Wanrooy E, Van Es T, Habets K, Hauer AD, et al. Immunomodulation of the inflammatory response in atherosclerosis. Curr Opin Lipidol 2007;18:521-6.
38. McCormick RK. Osteoporosis: Integrating biomarkers and other diagnostic correlates into the management of bone fragility. Alternative Medicine Review 2007;12:113-45.
39. Weitzmann MN, Pacifici R. The role of T lymphocytes in bone metabolism. Immunol Rev 2005;208:154-68.

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Screening points for a peripheral densitometer of the calcaneum for the diagnosis of osteoporosis

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Summary

We calculate specific triage thresholds for the PIXI-LUNAR heel densitometer to give a 90% specificity for osteoporosis and normal bone mineral density (BMD) at the hip or spine.

693 women aged 30-93 years (mean age 58.2 ± 9.6 years) referred for osteoporosis study, underwent hip and spine BMD measurements (HOLOGIC) by dual energy X-ray absortiometry (DXA), also had a peripheral heel DXA densitometry (PIXI-LUNAR). The os calcis T-scores for all woman were subjected to a receiver operator characteristic (ROC) analysis with the definition of osteoporosis (T-score ≤ -2.5) and BMD normal (T-score > -1) made at the the lumbar spine or femoral neck.

Patients with a heel T-score of above +0.6 are very likely to have normal bone density on axial densitometry, whilst patients with heel T-score of below -1.3 are very likely to have osteoporosis at the hip or spine. Only patients whose measurements lie between the thresholds should be referred for axial DXA.

Key words: *Bone mineral density, Osteoporosis, Peripheral x-ray absorptiometry.*

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Introduction

The prevalence of osteoporosis in white women over 50 years of age is high. In fact the risk of suffering an osteoporotic fracture of the hip, the spinal column or wrist over the course of their lives is 40%[1]. These facts make osteoporosis a real health problem. Bone mineral density (BMD) is the best prognostic factor of risk of osteoporotic fracture, for which reason densitometry is the fundamental technique for the diagnosis of osteoporosis before fractures appear.

Various techniques are available to measure BMD such as computerised tomography and ultrasound, but that most used currently is dual energy X-ray absorptiometry (DXA). The measurement of BMD through a DXA apparatus at the central level (hip and spinal column) is considered as a gold standard for the diagnosis of osteoporosis. The OMS developed some diagnostic criteria[2] based on the lowest of the densitometric results carried out on the hip and spinal column. The measurement of BMD in the peripheral skeleton is related to an added risk of fracture at whatever level[3]. Peripheral densitometers have the advantage of being of a lower cost to purchase, of needing less space for their installation, the tests of measurement are carried out with greater rapidity, and, due to their small size and weight, they are easy to transport. It has been observed that the cut-off points for the diagnosis of osteoporosis with axial densitometers are not the same as for peripheral densitometers[4-6]. The NOS (National Osteoporosis Society) recommends that peripheral densitometers are use as a screening tool with two cut-off points which identify those patients with spinal and/or hip osteoporosis, with a sensitivity and specificity of 90%[7]. In such a way the patients with peripheral BMD with a T-score below the lower cut-off point would have a high possibility of having osteoporosis in the hip or spine, and those having a T-score above the higher cut-off point would seldom have osteoporosis in the spine or hip. However, the cut-off points are different for the different peripheral densitometers[8]. It is not known if the cut-off points can change according to the population studied or whether it is dependent on the model of central densitometer with which it is compared.

The objective of this work is to find a diagnostic algorithm for postmenopausal osteoporosis in our population, combining a DXA peripheral densitometer of the calcaneum (PIXI-LUNAR) and a HOLOGIC central densitometer.

Material and methods

Central (of hip and spine) and peripheral (calcaneum) densitometries were carried out consecutively in 693 women referred to the rheumatology clinic for a study of postmenopausal osteoporosis. The study was approved by the scientific committee of our hospital. The central bone mineral density was measured with a Hologic Exploer™ Explorer® Series densitometer in the left femur and in the lumbar vertebra – L1 to L4. The bone mineral density in the calcaneum was measured in the left foot with a PIXI-Lunar densitometer. It was considered that a patient had osteoporosis if the T-score in the whole hip or in the lumbar region (L1-L4) was ≤ -2.5. A patient was classified as having normal BDM if the T-score was > 0 both in the hip and in the lumbar region. Using the statistical package SPSS 15.1 the sensitivity and specificity for the different T-scores, obtained through the peripheral densitometer, were calculated for the diagnosis of osteoporosis or normality by means of a ROC (receiver operator characteristic) curve, as were the Pearson correlation coefficient between the peripheral T-scores and those obtained in the hip and lumbar vertebrae. With this data the optimum cut-off points for screening were chosen. These points would have to comply at least with the recommendations of the NOS[7,8], which is to say a specificity and a sensitivity for the diagnosis of osteoporosis of 90%, with an interval of confidence which does not surpass the lower limit of 80%. In our diagnostic algorithm we consider it important to detect densitometries classified as normal, therefore for the upper cut-off point we would consider the T-score which would have a specificity of 90% to classify a patient with a normal central densitometry. In addition, the positive and negative predictive value of the cut-off points obtained for osteoporosis in our population would be calculated.

Results

The women studied had an average age ± standard deviation (SD) of 58.19 ± 9.61 years (30 and 93 years). The average height of the population studied was 155.8 ± 6.2 cm, the average weight 64.5 ± 10.7 kg and the BMI 26.9 ± 4.5 kg/m^2 (Table 1). The Pearson correlation coefficient was 0.616 between the T-scores obtained in the calcaneum and the whole hip, and 0.535 obtained with the lumbar vertebrae. According to the results of the axial densitometer (DXA) 29% of the women were osteoporotic, 47% osteopenic and 27% had normal levels of bone mass. By means of the ROC curve the sensitivity and specificity of the T-score obtained with the peripheral densitometer was calculated, to establish the diagnosis of osteoporosis and normality (Table 2). If a T-score of -2.5 SD is used in the peripheral densitometry for the diagnosis of osteoporosis the specificity is high, but the sensitivity is only 8%, which means that only 3% of densitometries will avoid being carried out. The specificity continues to be higher than 90% up to a cut-off point of T-score -1.3 SD, from which point the loss of specificity is significant (Figure 1A and Table 2). With this screening point only 4% of patients with normal axial densitometry would be classified as osteoporotic. Following the same criteria a T-score, using the PIXI, equal to or higher than 0.6 has a specificity of 90% to identify the normal central densitometries, and a sensibility of 97% to detect osteoporosis (Figure 1B and Table 2). With an algorithm based on the aforementioned cut-off points the positive predictive values

Table 1. Demographic characteristics of the different populations in which have been studied the cut-off points for different models of peripheral densitometers

Peripheral densitometer	Centre	n	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m²)
Osteometer DTX-200	London	393	62.6 (4.6)	160.8 (6.4)	66.2 (11.6)	25.6 (4.5)
Schick AccuDEXA	London	300	62.3 (4.7)	161.4 (6.5)	66.9 (12.5)	25.7 (4.9)
GE Lunar PIXI	Middlesbrough	213	62.8 (4.8)	158.1 (6.6)	64.1 (12.1)	25.6 (4.3)
Alara MetriScan	Hull	170	62.6 (4.5)	159.4 (6.5)	64.4 (10.8)	25.3 (3.9)
Demetech Calscan	Hull	140	62.2 (4.3)	159.3 (6.1)	65.1 (12)	25.7 (4.4)
Lunar PIXI	Valencia	693	57.9 (9)	155.8 (6.2)	65.4 (10.7)	26.9 (4.5)

Table 2. Sensitivity and sensibility of the PIXI of the calcaneum in establishing the diagnosis or osteoporosis or normality

T score PIXI	Osteoporosis		Normal	
	Sensitivity	Specificity	Sensitivity	Specificity
-2.5	8% ± 2%	99% ± 0.3%	100%	4% ± 2%
-1.6	36% ± 4%	95% ± 2%	99% ± 0.3%	20% ± 3%
-1.3	55% ± 4%	90% ± 2.5%	96% ± 2%	30% ± 4%
-1.0	66% ± 4%	82% ± 3%	94% ± 2%	40% ± 4%
-0.6	80% ± 3%	66% ± 4%	82% ± 3%	58% ± 4%
-0.2	90% ± 2%	51% ± 4%	68% ± 4%	70% ± 4%
0	94% ± 2%	45% ± 4%	63% ± 4%	76% ± 3%
0.2	95% ± 2%	38% ± 4%	74% ± 3.3%	81% ± 3%
0.6	97% ± 1.5%	25% ± 3.2%	45% ± 4%	90% ± 2%
1	97.5% ± 1%	16% ± 3%	30% ± 4%	94% ± 2%

Table 3. Cut-off points of different models of peripheral densitometers

Peripheral densitometer	Place of measurement	Higher T-score	Lower T-score	Axial Densitometer	% referred for axial BMD
Osteometer DTX-200	Forearm	-1.4 (-0.9 a -1.6)	-2.6 (-2.5 a -3)	Hologic	39% (34-44%)
Schick AccuDEXA	Hand	0.1 (0.9 a -0.2)	-1.6 (-1.4 a -2)	Hologic	44% (38-50%)
GE Lunar PIXI	Heel	-0.4 (0.2 a -0.6)	-2.0 (-1.6 a -2.6)	Lunar	49% (42-56%)
Alara MetriScan	Hand	-0.6 (0.1 a -1.1)	-2.4 (-2.1 a -2.7)	Lunar	48% (40-56%)
Demetech DXL Calscan	Heel	-1.4 -0.9 a -1.6)	-2.7 (-2.5 a -3.5)	Lunar	50% (41-59%)
Lunar PIXI (Valencia)	Heel	-0.2 (-0.1 a -0.3) 0.6 (0.8 a 0.45)*	-1.3 (-1.1 a -1.4)	Hologic	37 % (33-41%) 57% (53-61%)*

* 90% of specificity to detect normal bone mineral density

for the diagnosis of osteoporosis and normality would be 80% and 78% respectively in our population. The negative predictive value for the diagnosis of osteoporosis is 98% and for the diagnosis of normality, 98%. With this 43% ± 4% of central densitometries would be avoided. If we consider the recommendations of the NOS the cut-off point would be a T-score of -0.2 and less than -1.3 (Tables 2 and 3).

Discussion

The scarcity of axial densitometers has led to the use of peripheral densitometers in clinical practice, above all in the area of primary care. However, the clinical trials which have demonstrated the efficacy of different drugs in the treatment of osteoporosis, have been based on the selection of patients with low bone mineral density measured in the spine or hip. For this reason it is important to analyse the use of peripheral densitometers in the diagnosis of osteoporosis. The NOS[8] (Table 3) evaluated different models of peripheral densitometers and calculated the T-score cut-off points with which a sensibility and specificity of 90% for the diagnosis of osteoporosis with an axial densitometer would be obtained (Table 3). For each model two cut-off points were established, a T-score below which 90% of patients with osteoporosis centrally are classified and another T-score above which are found all those patients without densitometric osteoporosis, that is to say, with a T-score above -2.5 with the central densitometer. Central densitometries would only be carried out in those cases situated between the two cut-off points. The results of this work show that each model of peripheral densitometer had different cut-off points and, indeed, that they vary with age. Subsequently other authors have published results with other models of peripheral densitometers following the same methodology. McCauley et al.[9] determined the screening points of the Apollo Normand calcaneum densitometer with respect to a central lunar DPX-IQ densitometer. The T-score values were 9-1, 2 and -2.2.

Our results show different cut-off points with respect to a similar densitometer (PIXI-Lunar) analysed in the work of the NOS[8] (Table 3), above all in the lower cut-off point, which in our case was situated at -1.3 as opposed to at -2 obtained in the work of the NOS. There are various differences between the two works which could explain the discrepancies found. The women in our study had an average age of 58 ± 9 years (Table 1), slightly lower than the average of 62 years for the Pixi-Lunar group analysed in the NOS work. In their work they confirmed that in increasing the age of the population the cut-off points tend to result in a lower T-score[8]. On the other hand the central densitometers were different, a HOLOGIC in our work and a Lunar in the NOS study. Forham et al.[4], using a methodology similar to ours by means of ROC curves arrive at a cut-off point for detecting osteoporosis identical to ours, which is to say a T-score of -1.3 with a sensitivity of 69.6% for detecting osteoporosis and a specificity of 82.6%. They did not research the higher cut-off point. Pérez-Castrillón et al.[5] in a Spanish population arrived at the conclusion that the best cut-off point for the diagnosis of osteoporosis with a PIXI-LUNAR densitometer of the calcaneum is a T-score of -1.6 SD, even though their results are based on 58 patients on whom they carried out central and peripheral densitometry. The discrepancies which are observed between the different studies, in addition to being explained by the differences in models of peripheral and central densitometers used in each work, could relate to other variables such as age, number of patients included or prevalence of osteoporosis in the population studied[10]. For this reason screening points for different age ranges for each population where the peripheral densitometer might be used should be calculated.

On the other hand we preferred to change the criteria for determining the upper cut-off point with respect to that used by the NOS[7]. The risk of fracture is not a dichotomous variable, rather, it is continuous and the current trend is to calculate the absolute risk of fracture, with densitometry being an additional test, such as it is evaluated in the FRAX index[11]. With the algorithm proposed by the NOS[7,8] the cut-off point with a T-score of -0.2 in our peripheral densitometer has a specificity for normality of 70%, which is to say 30% of patients with osteopenia or osteoporosis are classified as non-osteoporotic, a fact which may restore credibility to the test among doctors and patients. In addition, a high percentage of fractures are produced in osteopenic patients and it is important to have this group of patients well classified[12]. With our cut-off point at a T-score of + 0.6, less than 10% of those patients with reduced BMD are classified as normal.

The National Osteoporosis Foundation[13] recommends treating those patients with osteoporosis diagnosed by central densitometry, and uses the risk of fracture calculated through the FRAX index to select those patients with osteopenia who are given treatment. Our algorithm is adapted to this scheme because it serves to detect with high sensitivity and specificity the patients with central osteoporosis by means of peripheral densitometry, while the majority of those who have osteopenia are evaluated through central densitometry.

A limitation in our study, equal to that of most studies published to date, is that the bone mineral density in the femoral neck has not been evaluated, nor that in the whole hip, and we do not know in which way this may modify the results.

The International Society for Clinical Densitometry (ISCD) recommends that the use of peripheral densitometry is limited to those cases in which access to central densitometry is lacking[10]. There are practically no studies on its utility in male osteoporosis and it is not valid to evaluate the efficacy of the treatment[10]. This fact contrasts with its wide use, for which reason the NOS[7] and the ISCD[10] have diffused the methodology to be applied, to ensure its trustworthiness as a screening tool in the

Figure 1A. ROC curve for the diagnosis of osteoporosis. Sensitivity (% of patients with osteoporosis detected by the PIXI) as against 1 – specificity (1- % of patients without osteoporosis classified as such). Area under the curve 0.816 (0.782-0.850)

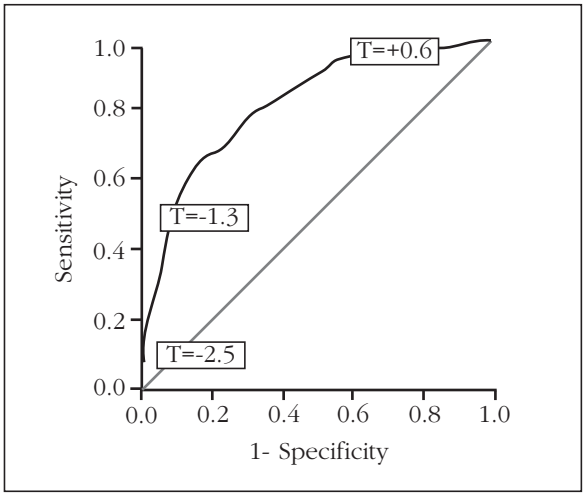
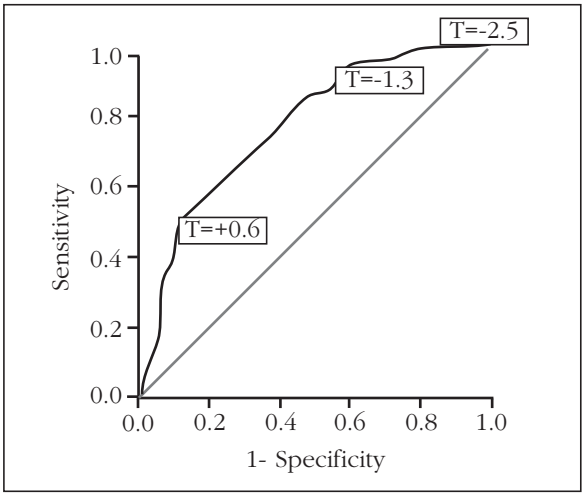


Figure 1B. ROC curve for the diagnosis of normal bone mineral density. Sensitivity (% of normal patients detected as such by the PIXI), 1- specificity (1- % of patients with osteopenia/osteoporosis detected as such by the PIXI). Area under the curve 0.773 (0.735-0.811)



diagnosis of osteoporisis, and it is in this context in which our study should be placed.

In conclusion, in our population of postmenopausal patients referred for the study of osteoporosis, a diagnostic algorithm of BMD based on two densitometers, one peripheral – PIXI-LUNAR, and the other central – HOLOGIC, enables 43% fewer central densitometries to be carried out. Those patients with a T-score with the peripheral densitometer between -1.3 SD and +0.6 SD are referred. The sensitivity of the algorithm for the detection of densitometric osteoporosis is 97% and of normality, 96%. With a specificity for both of 90%.

Bibliography

1. Melton LJ 3rd. How many women have osteoporosis now? J Bone Miner Res 1995;10:175-7.
2. World Health Organisation 1994 Assessment of Fracture Risk and its Application to Screening for Postmenopausal Oteoporosis. World Health Organization, Geneva, Switzerland, pp. 1-129.
3. Van der Klift M, Laet CDE, Pols HAP. Assessment of fracture risk: Who should be treated for osteoporosis? Beast Practice & Research Clinical Rheumatology 2005; 19:937-50.
4. Fordham JN, Chinn DJ, Kumar N. Identification of Women with Reduced Bone Density ar the Lumbar Spine and Femoral Neck using BMD at the Os Calcis. Osteoporos Int 2000;11:797-802.
5. Pérez-Castrillón JL, Martín-Escudero JC, del Pino-Montes J, et al. Prevalence of Osteoporosis Using DXA Bone Mineral Density Measurements at the Calcaneus. J Clin Densitom 2005;8:404-8.
6. Faulkner KG, Von Stetton, Miller P. Discordance in patient classification using T–scores. J Clin Densitom 1999;2:343-50.
7. National Osteoporosis Society (2004). Position statement on the use of peripheral x-ray absortiometry in the management of osteoporosis. National Osteoporosis Society, Bath, England.
8. Blake GM, Chin DJ, Steel SA, Patel R, Panayiotou E, Thorpe J, et al. A list of device-specific thresholds for the clinical interpretation of peripheral x-ray absorptiometry examinations. Osteoporos Int 2005;16:2149-56.
9. McCauley E, Mackie A, Elliot D, Chuck A. Heel Bone densitometry: device specific thresholds for the assessment of osteoporosis. Br J Radiol 2006;79:464-7.
10. Hans DB, Shepherd JA, Schwartz EN, Reid DM, Blacke GM, Fordham JN, et al. Peripheral Dual-Energy X- ray Absortiometry in the management of osteoporosis: The 2007 ISCD Official Positions. J Clin Densitom 2008;11:188-206.
11. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX and the assessment of fracture probability in men and women from the UK. Osteoporos Int 2008;19:385-97.
12. Siris E, Miller PD, Barret-Connor E, Faulkner KG, Wehren LE, Abbot TA, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women. Results from National Osteoporosis Risk Assessment. JAMA 2001;286:2815-22.
13. NOF's New Clinician's Guide to Prevention and Treatment of Osteoporosis. www.nof.org/professionals/Clinicians _Guide.htm Accessed April 18, 2008.

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Vertebroplasty: An alternative therapy for painful osteoporotic vertebral fractures which do not respond to conservative treatment? Review and update

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Summary
Purpose: To review and update the available literature of vertebroplastia: a procedure for treating painful compression fractures of the thoracic and lumbar spine that don't have responded to a conservative treatment.
Material and methods: A review of the literature was performed about the procedure, indications, complications and results based on PubMed and academic Google using the following keywords: vertebroplasty, compression vertebral fractures, polimetilmetacrilato, PMMA and osteoporosis.
Results: Description of the procedure, indications and complications. Several studies with few number of patients have indicated a high rate of successes an a low rate of complications. Recently, two double blind, randomized clinical trials have been published, comparing vertebroplasty with a simulation of it. The results of these studies don´t support the realization of vertebroplasty for the treatment of pain in osteoporotic compression fractures.
Conclusions: The clinical results of vertebroplasty were promising. Recently, the publication of two randomized clinical trials with greater evidence than previous ones, contradicts it.
Several questions without answer arise: Can this procedure be effective in a subgroup of patients? Could be effective in medium-long term? Are there other options to treat patients that don´t respond to conventional treatment?

Key words: *Vertebroplasty, Vertebral compression fractures, Polimetilmetacrilato, PMMA and Osteoporosis.*

Introduction

Osteoporosis has been called the silent epidemic of the 21st century. Fractures represent its most frequent complication. They can happen in any part of the body. Those of greater importance due to their consequences, costs and degree of incapacity are the vertebral, proximal femoral and distal radial. All add to the index of morbimortality, always produce a degree of incapacity and, in some case, increase mortality.

The prevalence of this disease means that approximately 40% of white women over 50 years of age and 13% of men, will suffer some osteoporotic fractures during their lives.

The vertebrae are the most common location. Thus, the EVOS study (European Vertebral Osteoporosis Study, a multi-centred European study), stated that in the European population over 50 years of age, one in five women and one in eight men had a vertebral fracture[1]. Similar results have been obtained in various epidemiological studies in different areas of Spain.

Around 60% of vertebral fractures (VF) are asymptomatic, for which reason the epidemiology is not known precisely. However, the EVOS study revealed that the incidence of VF is four times greater than fracture of the hip. It is estimated that in the year 2000 9 million osteoporotic fractures occurred in the world, of which 1.4 million were clinical VF. 34.8% of total fractures occurred in Europe, where the prevalence of VF is 12% at 60 years, and 25% in women and 17% in men at 75 years[2].

The prevalence of morphometric VF in the Spanish population over 50 varies between 15% and 27% in women[3-5]. One in four patients with VF will suffer a second VF during the following two years and 26% will suffer a non-vertebral fracture in the following year.

Various studies have shown that osteoporotic vertebral compression fractures represent an important cause of morbidity in patients affected by osteoporosis. It is estimated that in the United States some 700000 patients a year suffer from it, and it is expected that this incidence will increase in parallel with the increasing age of the population. It represents a significant economic cost of nearly 700 million dollars a year[6].

Even though, as has already been said, around 60% of vertebral fractures can be asymptomatic, it is also certain that one of the fundamental consequences of these fractures is pain, which can be intense, with disabling functional incapacity, which can be controlled with difficulty through non-invasive treatments (conventional analgesics, rest, physiotherapy…).

Since 1987, vertebroplasty (VP) has been developed as a reliable and minimally invasive alternative therapy.

Vertebroplasty is a minimally invasive technique which consists of an injection of a material (polymethylmethacrylate, calcium triphosphate, or other) into the body of a vertebra, with the aim of reducing the pain and augmenting its mechanical resistance.

The mechanism of its analgesic action is not clear. There are various hypotheses, notable among which is that the restoration of the mechanical integrity of the vertebra could mean a reduction in "micromovements" across the treated section, or that it is the result of local heat, chemical or vascular effects of the cement on the free nerve endings.

The substance most commonly used is polymethylmethacrylate (PMMA), a synthetic polymer used for the cementation of bone prostheses[7].

Procedure and technique

The procedure is carried out by puncturing the affected vertebral body, controlled fluoroscopically or by means of CAT (Computerised Axial Tomography), or both at the same time. There are four access routes to the vertebral bodies: anterolateral (for the cervical vertebrae), parapendicular, lateral (for the lumbar vertebrae only) and transpedicular. The last route is that most used.

The procedure is generally carried out with local anaesthetic and sedation, but epidural anaesthesia, rachianaesthesia or (very occasionally) general anaesthesia can be used. In VP the vertebral body is punctured using needles, through one of the aforementioned access routes, guided by means of digital fluoroscopy or CAT. Sometimes one can take advantage of the technique to carry out a biopsy if the aetiology of the vertebral fracture is not clear. When the needle reaches the third vertebral anterior, the cement mixture is injected under fluoroscopic control strictly to the posterior extension of the cement with the help of a mechanical injector[8] (Figure 1). There are various injecting devices on the market which, usually, mix the cement internally and connect direct to the needle (Figure 2).

The technique usually takes half an hour for each vertebra; it is not recommended that more than three vertebra are consolidated in a single session. The indications and contraindications of this technique are listed in Tables 1 and 2.

Results

There are various studies with a limited number of patients which, in general, demonstrate a high rate of success and a low rate of complications[9].

However, a systemic review published in 2006 to assess the efficacy and safety of the technique in osteoporotic vertebral fractures which included 1136 interventions in 793 patients, concluded that an evaluation of the efficacy of percutaneous vertebroplasty, would require clinical trials with long-term follow up. The level of pain measured using the VAS (Visual Analogue Scale) with a score of 0 to 10 improved significantly, from 7.8 to 3.1 (60.3%) immediately after the vertebroplasty. The short-term complications varied between 0.4% and 75.6%. The most frequent was the leak of cement out of the vertebral body (from 3.3% to 75.6%). Even though the majority were asymptomatic, in 2.4% they were devastating.

After the systematic review, the authors concluded that there was insufficient data to ensure efficacy. The procedure has a low rate of complications but those can be very severe. Of the 15 studies reviewed, 11 were prospective, 3 retrospective and only one a clinical trial[10].

Another recently published study compares the effects of optimum conventional treatment for pain against vertebroplasty in patients with vertebral compression fractures[11]. It consists of a prospective study, randomised, which evaluated the patients on day one and two weeks after, using the quality of life scale (QUALEFFO) and incapacity questionnaire (Roland-Morris Disability (RMD)). The study included 18 patients treated with vertebroplasty and 16 patients treated conventionally. Those patients in whom vertebroplasty had been carried out had an improvement in pain, mobility and functionality significantly better than those receiving conservative treatment.

Now in progress is the clinical trial VERTOS II[12], which intends to estimate the cost-effectiveness of vertebroplasty compared to conservative therapy in terms of the reduction in pain, quality of life, complications, secondary fractures and mortality. It consists of a multi-centric study, which intends to recruit 100 patients in each group, following up for 12 months. It is hoped that this study will greatly clarify current questions with respect to vertebroplasty.

The departments of radiology of the Mayo Clinic College of Medicine and the Baylo University Medical Center carried out a retrospective review of the first 1000 patients on whom they have carried out percutaneous vertebroplasty (independently of the underlying cause for which it was indicated), with the objective of putting together a prospective database.

Different variables were collected, including studies of images and of clinical visits, and they carried out telephone interviews with each patient. The study evaluated pain, on a subjective and visual scale, changes in mobility, the use of analgesic medication, and used incapacity questionnaires (Roland Morris Questionnaire). They found a dramatic improvement in all the parameters evaluated after vertebroplasty. The improvement in pain, mobility, use of analgesics and Roland-Morris score were evident immediately after vertebroplasty and remained for two years after follow up. There was a low level of complications after the procedure. The most frequent was rib fracture. In accord with these results, they conclude that professionals, in recommending this treatment for pain due to compression fracture, can inform patients that it is a technique with a high rate of success and a low rate of complications[13].

In spite of these studies suggesting a positive effect of treatment with vertebroplasty, compared with other conservative treatments, there are no randomised double blind clinical trials published.

Very recently the first two randomised double blind clinical trials have been published comparing vertebroplasty carried out with the injection of polymethylmethacrylate, with control patients on whom the procedure was carried out, but without the injection of this material.

Figure 1. Percutaneous vertebroplasty in the management of pain in vertebral compression fractures (De Asenjo JF, Brecha KM.)

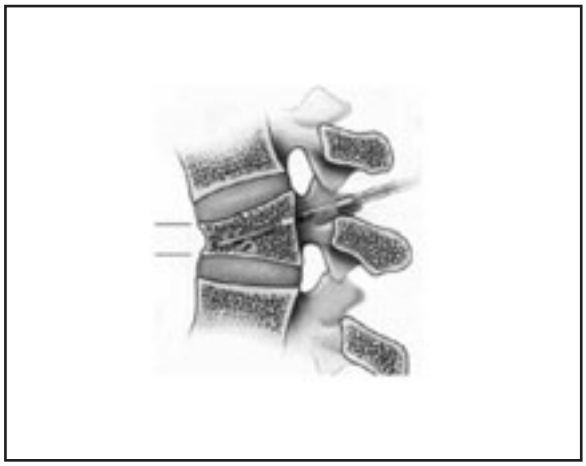

Figure 2. Injection and cementation devices

The INVEST study of Kallmes et al.[14], included 131 patients (vertebroplasty in 68 and simulation of vertebroplasty in 63). The results regarding pain and functional capacity after one month were similar in the treated and control groups, with a tendency towards an improvement in pain in the vertebroplasty group, although not significant. In both groups improvement was observed 3 days after the procedure, but were similar at 3 months. The authors concluded that the improvement in the pain and functional capacity associated with osteoporotic compression fractures in patients treated with vertebroplasty were similar to that in the control group. Another trial, Buchbinder et al.[15], included 71 patients (carrying out vertebroplasty in 35 and a simulation in 36). The results with regard to pain, quality of life and functional capacity after a week, and at I, 3 and 6 months, are similar in both groups. As before, the pain improved in both groups of patients.

These two trials had some limitations, fundamentally that they did not take into account other medical treatments which were taken and which could have affected the results.

Table 1. Indications for vertebroplasty

- Osteoporotic vertebral fractures with moderate to severe pain which does not respond to a normal analgesic treatment
- Painful vertebral metastasis
- Multiple myeloma with fractures in the vertebral body
- Painful haemangiomas of the vertebral body
- Painful osteonecrosis in the vertebral body
- Reinforcement of pathological vertebral body before stabilising surgery

Table 2. Contraindications

1. Absolute: a. Asymptomatic vertebral fractures b. Improvement with conservative therapy c. Local or systemic infection d. Non-correctable coagulopathy e. Myelopathy by intracanal bone fragment which comprises medulla f. Allergy to the cement or to the contrast contained in the cement
2. Relative: a. Fracture of the posterior wall of the vertebral body b. Tumour which invades the epidural space without causing neurological symptoms c. Compression fracture with diminution of vertebral height 0 or of > 75-80% d. Fractures older than one year

These findings question the indication of vertebroplasty for the treatment of patients with recent osteoporotic vertebral fractures.

Complications

The rate of complications described in the literature in the case of vertebroplasty in osteoporotic fractures, is low, between 1 and 3%. The most frequent is the leak of cement from the vertebra, the majority of times without clinical repercussions. On occasions severe complications have been described, such as infection, neurological failure after the leak of cement into the medullar canal[16], pulmonary embolism and pneumothorax, all with a very low frequency[17].

Occasionally hypertension and arrhythmia have been described, ascribed to the polymerisation of polymethylmethacrylate, for which reason cardiovascular monitoring is necessary continually during the procedure.

In the recently published clinical trials the rate of complications does not differ from those described previously.

Conclusions

Different series of published studies endorsed this technique as efficacious and safe, with a level of scientific evidence grade III.

Despite the fact that the clinical results of vertebroplasty were promising, the recent publication of two randomised clinical trials, with a higher grade of evidence than those published earlier, contradicts them.

The huge incidence of osteoporotic vertebral fractures which cause pain and significant incapacity in patients is an evident fact in numerous studies. The management of pain is a problem in daily clinical practice. We had confidence in the effectiveness and the very low rate of complications in this technique. After the publication of these clinical trials, questions are emerging which need to be answered: could the placebo effect of the simulated vertebroplasty through puncture and/or the effect of local anaesthetic be responsible for the similar results in both groups? And what of the superiority of the intervention, be it with cementation or simulated, over the conservative treatment? Could this technique be effective in a sub-group of patients as Kallmes et al. suggest? If this were the case, in which sub-group of patients? We have evidence of its lack of effectiveness in the short-to-medium-term, but in the long-term? In the face of the morbidity and incapacity which frequently produces secondary pain in these fractures, what other therapeutic alternatives do we have left for patients who don't respond to conventional treatment?

It is now even more important, if possible, to continue and/or carry out clinical trials which bring us answers to these questions.

And in the meantime? It becomes even more important to create a specialised and multidisciplinary approach around the management of pain. Likewise, adequate information and communication between the doctor and patient to evaluate the therapeutic options available, the current state of knowledge around this invasive technique and the possible risks and benefits, will permit the individualisation of the indication to the various alternative therapies

Bibliography

1. Bernard Pineda M, Garcés Puentes MV, Fernández Prieto A, Frutos Martinez R, Marin Aguilera B. Fractura vertebral aguda y técnicas de refuerzo vertebral. Reumatol Clin 2009;5(S2):32-5.
2. O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ y el European Vertebral Osteoporosis Study Group The prevalence of vertebral deformity in European men and women: the European Vertebral Osteoporosis Study. J Bone Miner Res 1997;11:1010-8.
3. Díaz López B, Naves Díaz M, Gómez Alonso C, Fernández Martín JL, Rodríguez Rebollar A, Cannata

Andía J. Prevalencia de fractura vertebral en población asturiana mayor de 50 años de acuerdo con diferentes criterios radiológicos. Méd Clin (Barc) 2000;115:326-31.
4. Naves M, Día-López JB, Gómez C, Rodríguez-Rebollar A, Cannata-Andia J. Determinants of incidente of osteoporotic fractures in female Spanish population older than 50. Osteoporosis Int 2005;16:2013-7.
5. Naves Díaz M, Díaz López B, Gómez Alonso C, Altadit Arregui A, Rodríguez Rebollar A, Cannata Andía J. Estudio de incidentic defracturas osteoporóticas em uma cohorte mayor de 50 años durante um período de 6 años de seguimiento. Méd Clin (Barc) 2000;115-650-3.
6. Kerr SM, Liechty B, Patel R, Harrop JS. Percutaneous vertebral compression fracture management with polyethylene mesh-contained morcelized allograft bone. Curr Rev Musculoskelet Med 2008;1:84-7.
7. Nicolás Macchiavello C, Ronald Schulz I, Marcos Ganga V. Vertebroplastia: puesta al día. Reumatología 2006;22(1):25-9.
8. Asenjo JF, Brecha KM. Vertebroplastia percutánea en el manejo del dolor de las fracturas vertebrales por compresión. Boletín El Dolor 2005;14:8-12.
9. Aslam E, Muhammad T, Sharif S. Percutaneous vertebroplasty in osteoporotic vertebral compression fractures: our initial experience. Percutaneous vertebroplasty in osteoporotic vertebral compression fractures: our initial experience. J Pak Med Assoc 2008;58(9):498-501.
10. Ploeg WT, Veldhuizen AG, The B, Sietsma MS. Percutaneous vertebroplasty as a treatment for osteoporotic vertebral compression fractures: a systematic review. Eur Spine J 2006;15(12):1749-58.
11. Voormolen MH, Mali WP, Lohle PN, Fransen H, Lampmann LE, van der Graaf Y et al. Percutaneous vertebroplasty compared with optimal pain medication treatment: short-term clinical outcome of patients with subacute or chronic painful osteoporotic vertebral compression fractures. The VERTOS study. AJNR 2007; 28(3):555-60.
12. Klazen CA, Verhaar HJ, Lampmann LE, Juttmann JR, Blonk MC, Jansen FH, et al. VERTOS II: percutaneous vertebroplasty versus conservative therapy in patients with painful osteoporotic vertebral compression fractures; rationale, objectives and design of a multicenter randomized controlled trial. Trials 2007;8:33.
13. Layton KF, Thielen KR, Koch CA, Luetmer PH, Lane JI, Wald JT, et al. Vertebroplasty, First 1000 Levels of a Single Center: Evaluation of the Outcomes and Complications. AJNR Am J Neuroradiol 2007;28:683-9.
14. Kallmes DF, Comstock BA, Heagerty PJ, Turner JA, Wilson DJ, Diamond TH, et al. A randomized trial of vertebroplasty for osteoporotic spinal fractures. N Engl J Med 2009;361:569-79.
15. Buchbinder R, Osborne RH, Ebeling PR, Wark JD, Mitchell P, Wriedt C, et al. A randomized trial of vertebroplasty for painful osteoporotic vertebral fractures. N Engl J Med 2009;361:557-68.
16. Yang SC, Chen WJ, Yu SW, Tu YK, Kao YH, Chung KC. Revision strategies for complications and failure of vertebroplasties Eur Spine J 2008;17:982-8.
17. Contreras O, Huete I. Vertebroplastia percutanea: nueva alternativa en el tratamiento del dolor de origen vertebral. Revista Chilena de Radiología 2003;9(2):45-50.

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Bone disease following liver transplant

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Summary
Liver transplant is now well established in the management of chronic terminal hepatopathy. With the follow up of these patients, we are getting to know pathologies derived from their earlier diseases and those from the organ transplant, among which are those produced by the immunosuppression (cyclosporine, FK506, sirolimus, glucocorticoids) necessary for their treatment. Among these complications with affect the quality of life in these patients are osteoporosis and fractures, which can appear mainly in the first 6-12 months after transplant, but which can continue to a lesser extent in the following years. Vertebral fractures, and those of the ribs, are the most frequent, in 65% and 24% of patients, with negative prognostic factors such as age and primary biliary cirrhosis. So, it is a severe form of osteoporosis which is analysed in this work, and to which we bring our therapeutic experience. With antiresorptive drugs, positive results have been reported for the prevention and treatment of this bone loss.

Key words: *Osteoporosis, Liver transplant, Biphosphonates, Steroids.*

Introduction

In this review the factors which can influence the loss of bone mass after transplant, at least in patients with chronic hepatopathy, are outlined. The review goes on to study the factors which intervene in the post-transplant loss of bone mass and in the appearance of fractures. Finally we analyse the management of those patients at risk of post-transplant osteoporosis and review the current scientific evidence for antiresorptive treatment in this scenario.

Pre-transplant bone pathology

Loss of bone is a frequent complication of chronic hepatopathy, its prevalence being higher among those patients on the waiting list for a liver transplant, especially in cholestatic hepatopathy[1-3]. There are multiple associated risk factors, among which are: hypogonadism, vitamin D deficiency, malabsorption, low weight, reduced physical activity, and in some cases, previous steroid treatment.

The last two decades have brought significant changes in the management of chronic hepatopathy, in immunosuppression regimes, in waiting times for liver transplants, and in the nutritional status of patients. Some authors have observed an improvement in lumbar bone mineral density (BMD) with pre-transplant T-scores increasing from -2.5 before 1990 to -1.7 after 1996[2].

Bone mass in the post-transplant period

After the transplant an accelerate loss of bone tales place in the first 3-6 months, increasing considerably the incidence of osteoporosis and osteopenia[2,4-7]. A number of studies show that this early loss of bone is followed by a recuperation of bone metabolism which starts just a few months are the transplant[8,9]. Although the first post-transplant studies showed a predominance of lumbar bone loss and vertebral fractures[10], more recent studies indicate a greater loss of bone in the femur[11]. In addition, differently from bone loss in the lumbar region, the femoral bone loss persists for the first three years after the transplant[2,7]. Other works have found this decrease in BDM in the femoral neck at 6 and 12 months, even despite treatment with biphosphonates, which suggest a lesser effect of these drugs in cortical bone[12].

Factors implicated in the loss of bone mass

Glucocorticoids

Given that the early loss of bone mass has been observed in all transplants of solid organs, it has traditionally been assumed that the high doses of glucocorticoids (GC) necessary for immunosuppression played a principal role in this loss[5,6].

The potential impact of the dose of GC as a determinant of the loss of bone is supported by the absence of bone loss in the lumbar and proximal femoral regions found in patients with renal transplants treated with low doses of steroids and tacrolimus[13]. In addition, in the work of Martínez et al.[14], the withdrawal of GC after the transplant accelerated the recuperation of lumbar BMD (Z-score -0.44 in the group with early withdrawal of prednisone vs Z-score of -0.99 in patients in whom treatment with prednisone was maintained; $p< 0.05$), without adverse effects on tolerance of the graft. On the other hand, the higher rates of fracture which are present after heart and lung transplants[15,16], in which greater doses of steroids are used, would be consistent with the role which they play in the pathogenesis of post-transplant osteoporosis. In spite of the fact that few works have successfully shown an association between the cumulative dose of GC and the loss of bone mass in the post-transplant period[17,18], Guichelaar et al.[8], confirmed this relationship by means of a histomorphometric analysis. In this work, the accumulated dose of steroids at one month and 4 months post-transplant, was positively correlated with the loss of bone volume, and inversely with the parameters of formation. In addition, this histomorphometric study indicated that the principal incident which drives the loss of bone mass happens very early in the post-transplant period and, probably, is found to be related to a reduction in bone formation. These findings are consistent with the known effect of steroids on the osteoblasts and on bone formation. For the same reason, the transitory inhibition of the bone formation can play a key role in the loss of bone following transplants.

The same group[19], in a study or 33 patients with chronic cholestatic hepatopathy found that despite a decrease in BMD 4 months after transplant, biopsies of the iliac crest at 4 months showed histomorphometric improvement, increasing significantly the static and dynamic parameters from low levels at the moment of transplant to values in the range of normality 4 months after the transplant. At the same time, the measurements at four months of the parameters for bone resorption showed the same increase, but in a range similar to those values obtained immediately post-transplant. These histomorphometric findings indicate that despite the post-transplant loss of bone, at 4 months the bone metabolism had improved, with an increase in bone formation and a more closely matched balance of formation and resorption.

The current evidence, for the same reason, suggests that the loss of bone after liver transplant is caused by an initial increase in bone resorption, together with a decrease in formation. Later, the bone formation increases and may overtake the resorption. These changes could be consistent with the rapid decrease in BMD observed in the first months post-transplant, and the later recuperation towards baseline values, found in the majority of studies.

Other immuppressive drugs

The role played by other immunosuppressive drugs in the post-transplant loss of bone mass is not well known. Tacrolimus induces severe loss of trabelucar bone in rats, although it seems to be less severe in humans[20]. With respect to cyclospo-

rine A (CyA), some studies in humans show a similar effect as that observed in murine models in patients with liver, kidney and heart transplant[17,21,22]. Mofetil mycophenolate has not shown any effects on the bone in murine models.

In a study of 360 patients with liver transplants for chronic cholestatic hepatopathy the post-transplant bone gain was less and the number of fractures greater in patients treated with CyA than those treated with tacrolimus[24]. Other authors have shown that patients who receive CyA have more fractures than those with tacrolimus, but this effect may reflect the differences in the average dose of steroids between the two groups[18].

In another study, although the losses of bone mass were similar in patients treated with CyA than in those treated with tacrolimus, the histomorphometric changes after transplant suggest that patients receiving tacrolimus can have a more rapid recuperation in bone metabolism after the initial phase of bone loss, in comparison with patients with CyA[8]. In in vivo studies, both CyA and tacrolimus alter the balance of bone remodelling, with resorption exceeding formation, with the consequent loss of bone mass. On the other hand, in relation to CyA, this bone loss could be seen to be being powered by the decrease in blood levels of testosterone which it provokes in the patients[20].

Vitamin D

Numerous works in the literature found low levels of 25-OH vitamin D in hepatopathic patients. Although it has been suggested that the decreased levels of vitamin D in patients with hepatopathies might be due in part to a lower production of transport proteins (DBP and albumin)[25,26], to a change in the 25 hydroxylation of vitamin D[27-29], or to the malabsorption of liposoluble vitamins in cholestatic hepatopathies[30], it seems that the lower levels of vitamin D in chronic hepatopathies are related, with great probability, to a deficient supply of vitamin D due to environmental and dietary factors.

Some authors found that the levels of 25-OH vitamin D are independent predictors of the BMD in the hips of patients with cirrhosis[31]. Crosbie et al. found a correlation between levels of 25-OH vitamin D at 3 months after liver transplant and an increase in BMD at 6 months, which suggests that the normalisation of levels of vitamin D can exert a positive effect on BMD[9].

Fractures in the post-transplant period

In patients receiving a liver transplant, the most frequent fractures are vertebral fractures. The following risk factors for fractures occurring after transplants have been identified: advanced age[7]; pre-transplant vertebral fractures[31]; chronic cholestatic hepatopathies[10]. Similarly to that which was the case with bone mass, few authors have found a relationship between the dose of glucocorticoids and the risk of fracture in patients receiving a liver transplant[24].

Guichelaar et al. studied, in 360 patients with chronic cholestatic hepatopathy between 1985 and 2001, the incidence and predictive variables of fractures (vertebral and non-vertebral) pre- and post-transplant, from the pre-transplant period, up to 8 years after[24]. The accumulated incidence of fractures was 30% in the first year post-transplant and 46% at 8 years after the transplant. Differently from other studies, there was a similar incidence of vertebral and non-vertebral post-transplant fractures. The majority of fractures occurred in trabecular bone, with the spinal column and the ribs making up over 90% of the total fractures. The principal risk factors for the appearance of fractures post-transplant were the presence of fractures pre-transplant, a lower BMD, the dose of glucocorticoids post-transplant and primary biliary cirrhosis. Neither the loss of bone in the first 4 months post-transplant, nor the later bone gain were correlated with fractures.

The estimates of fragility-related fracture post-transplant varied widely according to the studies. In various works the percentages of fractures referred varied between 25-35%, mainly in the first 6 months after the transplant[4,7,32,33], while other authors found a lower rate of fractures (6-8%)[11,34,35]. These differences in the incidence of fractures referred to in the different studies could be due to a number of factors: the selection of the patients, treatment with immunosuppressors, criteria used for the diagnosis of vertebral fractures. However, in general, the highest rates of fractures appear in the literature in the earlier works, while more recent works report lower rates. Compston found an incidence of 27% for vertebral fractures in the first three months after transplant in a study of 37 patients receiving a liver transplants between 1993 and 1995[32]. In a later study of the same group carried out between 1995 and 1998 the incidence of fractures in the first year was only 5%[11]. Between these studies there was a significant reduction in the dose and duration of treatment with glucocorticoids, although the use of cyclosporine and tacrolimus was hardly modified.

Thus, it appears that the natural history of post-transplant osteoporosis has been improving in the last few years. Other factors which might explain this apparent reduction on the frequency of osteoporotic post-transplant fractures as well as the reduction in the doses of glucocorticoids (and possibly the use of cyclosporine A, which has been substituted by other immunosuppressant drugs), could be that in some countries transplants nowadays take place at an earlier stage of hepatopathy, which diminishes the prevalence of pre-transplant bone pathology. In addition, the spectrum of hepatopathies in which transplants are carried out has changed over the years. Thus, in Europe primary biliary cirrhosis represented 57% of the transplants in 1983, whilst in 1999 this was only 20%, with an increase in patients receiving transplants due to viral hepatitis (principally VHC) and alcoholic cirrhosis.

Evaluation of patients at risk of post-transplant osteoporosis

The adequate management of post-transplant bone pathology implies both the optimisation of bone health before transplant and the prevention of bone loss after transplant. In summary, the following paths of intervention are recommended[10,36].

1. Pre-transplant period

Table 1 summarises the initial evaluation of a patient with chronic hepatopathy on the waiting list for a liver transplant. The following biochemical analyses are carried out: calcium, phosphorus, total and bone phosphatase, creatinine, calcidiol, PTH, TSH, proteinogram, total testosterone, bio-available testosterone and LH or oestradiol and FSH, as well as calciuria in urine in 24 hours. Annual bone densitometry before transplant. Lateral X-ray of the dorsolumbar spinal column. Moderate physical exercise is recommended. The maintenance of a good nutritional state. Ensure an adequate intake of calcium (1500 mg/day) and vitamin D (400-800 UI/day) (ensure adequate blood levels of 25-OH vitamin D). Prevent hypercalcuria (if a patient who does not take loop diuretics has hypercalcuira, add 25 mg/day of hydrochlorothiazide). Treat hypogonadism if present and not contraindicated.

After a first evaluation, the follow up of the patient should be oriented around the results of the BMD, the existence or not, of fractures, as well as other associate risk factors.

2. Prevention of bone loss post-transplant

In general, for the prevention and treatment of post-transplant osteoporosis the use of biphosphonates is recommended[36]. While there are contradictory data for both oral and intravenous biphosphonates, many studies with favourable results for biphosphonates were carried out without randomisation, without a control group and with a small number of patients, such that the beneficial effect can be attributed incorrectly to the treatment and is due to the general improvement in the state of the patient which takes place after the transplant.

Given the accelerate loss of bone mass which occurs immediately after transplant, many experts recommend preventative treatment for all patients receiving transplant of solid organs, independently of the BMD pre-transplant[23,33,36,37]. This approach is based on observational data which show an overlap in pre-transplant BMD values between patients who present post-transplant fracture and those who do not[15]. Another approach for the management of patients receiving transplants is to apply clinical guides used for the prevention of osteoporosis induced by glucocorticoids.

Preventative measures and antiresorptive treatment after liver transplant. Current evidence.

The studies around the efficacy of treatment with vitamin D in patients with cirrhosis have a number of shortcomings: lack of randomisation and control group, low numbers of patients, predominance of primary bilial cirrhosis, poor representation of viral hepatitis, absence of data on fractures[38]. Although the works published to date do not allow the conclusion to be drawn that treatment with vitamin D influences the progression of bone disease in patients with cirrhosis, almost all authors, including the American Association of Gastroenterology, recommend supplementation with calcium and vitamin D in this type of patient[26,30]. Supplementation with calcium and vitamin D is also recommended during the post-transplant period. Table 2 summarises the characteristics and results of the main studies on which we are going to comment.

Hay et al. found that subcutaneous calcitonin (100 UI/day) was not successful in preventing bone loss or fractures in patients with primary bilial cirrhosis or primary schlerosing cholangitis receiving liver transplants[39]. In another work of Guichaar et al., in those with liver transplants histomorphometric analysis showed that calcitonin (n= 14 calcitonin, n= 19 control) was not effective, either directly (number of osteoclasts, area of erosion) or indirectly (trabecular thickness, number and separation) on the parameters for bone resorption[8].

Valero et al.[41] studied the effects of calcitonine vs cyclical etidronate on the lumbar BMD in 40 patients with liver transplants. There was a significant increase in BMD in both groups, but greater in the group with etidronate[40]. Another study with cyclical etidronate, combined with alphacalcidiol and calcium, carried out in 53 patients did not find prevention of bone loss in the lumbar or femoral region, although neither was there a control group[41].

With respect to pamidronate, the results are contradictory. One non-randomised study found a positive effect in the reduction of vertebral fractures in 13 patients with liver transplants[42]. In Dodidou et al.[44,21] patients with liver transplants and 13 with heart transplants with high levels of loss of bone mass or osteoporotic fractures occurring in the first two years after the transplant received 30 mg/3 months of intravenous pamidronate over two years, along with 1000 mg of calcium and 1000 UI/day of vitamin D[43]. A historic control group of 58 patients treated with calcium and vitamin D was used. The BMD increased significantly in the lumbar spinal column and femoral neck among those patients treated, in spite of the fact that the treatment was not initiated immediately after the transplant. Another non-randomised study with pamidronate carried out by Pennisi et al. involved 85 patients receiving liver transplants. 47 of these patients, who presented with pre-transplant osteopenia or osteoporosis, received 30 mg of i.v. pamidronate every 3 months for one year after the transplant. The rest of the patients were used as the control group. A significant increase in BMD in the lumbar region was observed in patients treated with pamidronate as opposed to the control group. The BMD in the femoral neck reduced in both groups. The authors concluded that pamidronate appears to have a

limited effect on trabecular bone without modifying the cortical structure of the femur[44]. Ninkovic et al., in a controlled and randomised study in 99 patients with liver transplants, an i.v. infusion of 60 mg of pamidronate, administered preoperatively, had no significant effect on the loss of bone mass, or on the rate of fractures one year after the transplant[11]. An unexpected finding of this study was the absence of loss of lumbar bone mass and the low rate of fractures (8%) in the non-treated patients, although there was significant loss of bone in the femoral neck, which pamidronate could also not prevent. In a recent multi-centred study by Monegal et al., with 79 patients, two infusions of 90 mg of i.v. pamidronate (in the first two weeks, and 3 months after liver transplant) prevented the loss of bone mass in the lumbar region during the first year. Pamidronate did not manage to reduce the loss of bone in the femoral neck or the incidence of post-transplant fractures[12].

With respect to the data on alendronate, Millonig et al. studied, for an average of 27.6 months, 136 patients who had received liver transplants. All the patients received 1000 mg of calcium and 400 UI of vitamin D. In addition, those who presented with osteopenia or osteoporosis took alendronate weekly. The BMD in the lumbar region and in the femoral neck increased in the patients with osteoporosis[45]. Atamaz et al., in the first randomised study with a control group carried out with alendronate weekly, in 98 patients with liver transplants, during 24 months of follow up, observed that alendronate (70 mg weekly) significantly increased bone mass in the lumbar region, in the femoral neck and in the whole hip, as opposed to calcium (1000 mg) and calcitriol (0.5 μg), however it did not appear to exert a protective effect against fractures[46].

As far as zoledronate is concerned, in a study by Crawford, 62 patients with liver transplants were referred, randomly, to receive zoledronic acid (4 mg i.v.) or a placebo 7 days after transplant and at[1,3,6] and 9 months post-transplant. All the patients received 600 mg/day of calcium carbonate and 1000 UI/day of vitamin D. The group with zoledronic acid lost significantly less bone mass in the hip. In the lumbar region, the group with zoledronate lost less bone mass at three months, but the significant difference between the two groups had disappeared at 12 months. A notable finding of this study was the recuperation of the lumbar BMD at 6 months in the placebo group, which almost reached baseline levels after a transitory reduction at 3 months. At 12 months, the values of BMD superseded baseline levels in both the placebo group as well as in the group receiving zoledronate[35]. This spontaneous improvement in BMD in the placebo group could be related to a general improvement in the state of those patients, mobility, muscle mass and nutrition, as a consequence of an improved liver function[7,10]. In the same study, Crawford observed a higher loss of bone mass in the hip than in the lumbar region in the placebo group, reaching the nadir 6 months after the transplant with partial recuperation later[35]. The patients who received treatment with zoledronate did not show loss of bone mass in the hip. In another study by Bolingbauer, the patients received treatment with 8 infusions of 4 mg of zoledronic acid i.v., over the first 12 months after their liver transplant (one infusion per month for the first 6 months, another at 9 months and another at 12 months), in addition to calcium carbonate (1000 mg/day) and vitamin D (800 UI/day) The main target of the study – fractures in the first 24 months after transplant – was found in 4 patients (8.5%) from the group with zoledronate (n= 47), and in 11 patients (22.5%) in the control group (calcium + vitamin D) (n= 49) (p= 0.05). The densitometric parameters were significantly better in the femoral neck in the group with zoledronate only at 6 months, being similar in both groups later. In terms of the lumbar spinal column, no differences between the groups were found, neither at 6 nor at 12 months[47]. The same group published a subsequent work, carried out with the same patients as in the earlier study in which they analysed through histomorphometry the parameters of distribution of the density of bone mineralization at the time of transplant. 39 patients were studied, 21 in the zoledronate group and 18 in the control group. Six months after the transplant, the treatment with 4 mg/month zoledronate i.v., showed a significant reduction in bone turnover compared with those patients treated with calcium and vitamin D (n= 18) as well as a definite restoration in mineralization[48]. This improvement in the bone-

Table 1. Initial evaluation of a patient with chronic hepatopathy on a waiting list for liver transplant

Initial pretransplant evaluation
Biochemical determinations: -Calcium, phosphorus, total and bone alkaline phosphatase, creatinine, 25-OH vitamin D, PTH, TSH, proteinogram -Total and bioavailable testosterone and LH/oestradiol and FSH -Urinary calciuria 24 h
Lumbar and hip BMD annually
Lateral X-ray of dorsolumbar spinal column
Moderate physical exercise
Maintain good nutritional state and ensure adequate blood levels of 25-OH vitamin D
Prevent hypercalciuria
Treat hypogonadism if present and if there are no contraindications
Initiate antiresorptive treatment according to BMD, fractures and other risk factors

Table 2. Summary of main studies with biphosphonates in the liver transplant

	n	Design	Type of patients	Start treatment	Duration of treatment	Biphosphonate group	Control group	BMD	Fracture incidents*
Alendronate Milonig, 2005 (46)	136 98 ALN (OP or op) 38 cont	Non-controlled Non-randomised	55±9 years Patients with OP or op receive ALN OP 23.5% op 48.5%	0-4 months postx	Average 27.6 months	ALN 70 mg/weekly v.o. 1000mg calcium/d 400 UI vitD/d	(patients without OP or op) 1000mg calcium/d 400 UI vitD/d	Increase in DMO CL in osteoporotics at 24 months (% not specified) Increase in DMO CF in osteoporotics between 4 and 12 months in osteopenics between 24 and 36 months (% not specified)	total 5.8% (not specified by group)
Alendronate Atamaz, 2006 (47)	98 49 ALN 49 cont	controlled randomised open	44±10 years ALN T-score CL: -1.6±0.9 CF: -1.3±0.8 cont T-score CL: -1.5±0.8 CF: -1.2±0.7	First month postx	24 months	ALN 70 mg/weekly v.o. 1000mg calcium/d 0.5mcg calcitriol/d	1000mg calcium/d 0,5mcg calcitriol/d	ALN vs control CL 24 months 8.9±5.7% vs 1.4±4.9% p<0.05 CF 24 months 8,7±4,8% *vs.* 0,6±4,5% p<0,05	 ALN 3 cont 11 n.s.
Pamidronate Ninkovic, 2002 (11)	99 45 PM 54 cont	controlled randomised open	52±11 años OP 34%	pretx- 3months postx	12 months	PM 60 mg i.v. Single dose	no treatment	No difference between Groups CL (vs baseline) with +1.9% p<0.01 CF (vs baseline) PM -5.2% p<0.01 with -2.3% p<0.01	 PM 4 cont 2 n.s.
Pamidronate Pennisi, 2006 (45)	85 47 PM (OP or op)	controlled Non-randomised	54±10 años Patients with OP or op recei ve PM % not specified	Not specified	12 months	PM 30 mg iv/3months calcium 1000mg/d	calcium 1000mg/d vit D 800 UI/d	CL T-score (vs baseline) PM +1.07 p<0.01	 PM 1

Table 2. Summary of main studies with biphosphonates in the liver transplant (cont.)

	n	Design	Type of patients	Start treatment	Duration of treatment	Biphosphonate group	Control group	BMD	Fracture incidents*
	38 cont					vit D 800 UI/d		CF T-score (vs baseline) PM -0.20 con -0.35 p<0.01	cont 3 n.s.
Pamidronate Monegal, 2008 (12)	79 38 PM 41 cont	controlled randomised Double blind multicentric	53±11 years PM 55%op 31%OP con 59%op 37%OP	2 weeks postx	12 months	PM 90 mg i.v. (2 weeks postx 3 months postx) calcium 1000mg/d 25OHD 16000 UI/15d	calcium 1000mg/d 25OHD 16000 UI/15d	CL DMO vs baseline PM +2.9% p<0.02 CF DMO vs baseline PM -3.2% con -3.1% p<0.01	 PM 7 con 3 n.s.
Zoledronate Crawford, 2006 (37)	62 32 ZLN 30 cont	controlled randomised Double blind 2 centres	47±10 ZLN 32%op 18%OP control 50%op 10%OP	1 week postx	12 months	ZLN 4 mg i.v. (1 week, months 1,3,6,9) calcio 600 mg/d vit D 1000 UI/d	calcium 600 mg/d vit D 1000 UI/d	% change DMO ZOL-con CL n.s CF n.s FT +2,4% p<0.05	 ZLN 2 cont 2 n.s.
Zoledronate Bodingbauer, 2007(48)	96 47 ZOL 49 cont	controlled randomised open	52±8 ZOL T-score CL -1.29 CF -1.23 cont T-score CL -1.12 CF -1.41	1 month postx	24 months	ZLN 4 mg i.v. (months postx 1,2,3,4,5,6,9 y 12) calcium 1000mg/d vit D 800 UI/d	calcium 1000mg/d vit D 800 UI/d	Objetive 2º no difference between groups	Objetive 1º ZLN 4 con 11 p=0.05

BMD: bone mineral density; OP: osteoporosis; op: osteopenia; ALN: alendronate; PM: pamidronate; ZLN: zoledronate; con: control; CL: lumbar spinal column; CF: femoral neck; FT: femur total.
*vertebral and non-vertebral fractures due to fragility

's micro-architectural properties may explain the beneficial effect of treatment with zoledronate on the risk of fracture observed two years after the transplant, despite not achieving an improvement in the BMD with respect to the control group.

In conclusion, although the transplant of organs, in particular liver transplants, have contributed to resolving the vital problem of terminal chronic hepatopathies, the combination of the previous disease, and the intervention with immunosuppressive measures, can facilitate the development of an accentuated bone loss, which is going to impact on the future quality of life of these patients. At present we count on effective drugs for the prevention and treatment of this osteoporosis. New anti-osteoporotic drugs which stimulate bone mass, should be studied and trialled in this pathology. Finally, a better knowledge of the mechanisms by which immumosuppressors induce this bone loss is going to be important for its better prevention and etiopathogenic treatment.

Bibliography

1. Ninkovic M, Love SA, Tom B, Alexander GJ, Compston JE. High prevalence of osteoporosis in patients with chronic liver disease prior to liver transplantation. Calcif Tissue Int 2001;69(6):321-6.
2. Guichelaar MM, Kendall R, Malinchoc M, Hay JE. Bone mineral density before and after OLT: long-term follow-up and predictive factors. Liver Transpl 2006;12(9):1390-402.
3. Floreani A, Mega A, Tizian L, Burra P, Boccagni P, Baldo V, et al. Bone metabolism and gonad function in male patients undergoing liver transplantation: a two-year longitudinal study. Osteoporos Int 2001;12(9):749-54.
4. Eastell R, Dickson ER, Hodgson SF, Wiesner RH, Porayko MK, Wahner HW, et al. Rates of vertebral bone loss before and after liver transplantation in women with primary biliary cirrhosis. Hepatology 1991;14(2):296-300.
5. Rodino MA, Shane E. Osteoporosis after organ transplantation. Am J Med 1998;104(5):459-69.
6. Leidig-Bruckner G, Hosch S, Dodidou P, Ritschel D, Conradt C, Klose C, et al. Frequency and predictors of osteoporotic fractures after cardiac or liver transplantation: a follow-up study. Lancet 2001;357(9253):342-7.
7. Monegal A, Navasa M, Guanabens N, Peris P, Pons F, Martinez de Osaba MJ, et al. Bone disease after liver transplantation: a long-term prospective study of bone mass changes, hormonal status and histomorphometric characteristics. Osteoporos Int 2001;12(6):484-92.
8. Guichelaar MM, Malinchoc M, Sibonga J, Clarke BL, Hay JE. Immunosuppressive and postoperative effects of orthotopic liver transplantation on bone metabolism. Liver Transpl 2004;10(5):638-47.
9. Crosbie OM, Freaney R, McKenna MJ, Curry MP, Hegarty JE. Predicting bone loss following orthotopic liver transplantation. Gut 1999;44(3):430-4.
10. Compston JE. Osteoporosis after liver transplantation. Liver Transpl 2003;9(4):321-30.
11. Ninkovic M, Love S, Tom BD, Bearcroft PW, Alexander GJ, Compston JE. Lack of effect of intravenous pamidronate on fracture incidence and bone mineral density after orthotopic liver transplantation. J Hepatol 2002;37(1):93-100.
12. Monegal A, Guanabens N, Suarez MJ, Suarez F, Clemente G, Garcia-Gonzalez M, et al. Pamidronate in the prevention of bone loss after liver transplantation: a randomized controlled trial. Transpl Int 2009;22(2): 198-206.
13. Goffin E, Devogelaer JP, Depresseux G, Squifflet JP, Pirson Y. Osteoporosis after organ transplantation. Lancet 2001;357(9268):1623.
14. Mart G, Gomez R, Jodar E, Loinaz C, Moreno E, Hawkins E. Long-term follow-up of bone mass after orthotopic liver transplantation: effect of steroid withdrawal from the immunosuppressive regimen. Osteoporos Int 2002;13(2):147-50
15. Shane E, Rivas M, Staron RB, Silverberg SJ, Seibel MJ, Kuiper J, et al. Fracture after cardiac transplantation: a prospective longitudinal study. J Clin Endocrinol Metab 1996;81(5):1740-6.
16. Shane E, Papadopoulos A, Staron RB, Addesso V, Donovan D, McGregor C, et al. Bone loss and fracture after lung transplantation. Transplantation. 1999;68(2):220-7.
17. Giannini S, Nobile M, Ciuffreda M, Iemmolo RM, Dalle Carbonare L, Minicuci N, et al. Long-term persistence of low bone density in orthotopic liver transplantation. Osteoporos Int 2000;11(5):417-24.
18. Monegal A, Navasa M, Guanabens N, Peris P, Pons F, Martinez de Osaba MJ, et al. Bone mass and mineral metabolism in liver transplant patients treated with FK506 or cyclosporine A. Calcif Tissue Int 2001;68(2): 83-6.
19. Guichelaar MM, Malinchoc M, Sibonga JD, Clarke BL, Hay JE. Bone histomorphometric changes after liver transplantation for chronic cholestatic liver disease. J Bone Miner Res 2003;18(12):2190-9.
20. Epstein S. Post-transplantation bone disease: the role of immunosuppressive agents and the skeleton. J Bone Miner Res 1996;11(1):1-7.
21. Bone histology in renal transplant patients receiving cyclosporin. Lancet 1988;1(8593):1048-9.
22. Thiebaud D, Krieg MA, Gillard-Berguer D, Jacquet AF, Goy JJ, Burckhardt P. Cyclosporine induces high bone turnover and may contribute to bone loss after heart transplantation. Eur J Clin Invest. 1996;26(7):549-55.
23. Maalouf NM, Shane E. Osteoporosis after solid organ transplantation. J Clin Endocrinol Metab 2005;90(4): 2456-65.
24. Guichelaar MM, Schmoll J, Malinchoc M, Hay JE. Fractures and avascular necrosis before and after orthotopic liver transplantation: long-term follow-up and predictive factors. Hepatology 2007;46(4):1198-207.
25. Bikle DD, Halloran BP, Gee E, Ryzen E, Haddad JG. Free 25-hydroxyvitamin D levels are normal in subjects with liver disease and reduced total 25-hydroxyvitamin D levels. J Clin Invest 1986;78(3):748-52.
26. Crawford BA, Labio ED, Strasser SI, McCaughan GW. Vitamin D replacement for cirrhosis-related bone disease. Nat Clin Pract Gastroenterol Hepatol 2006;3(12): 689-99.
27. Compston JE. Hepatic osteodystrophy: vitamin D metabolism in patients with liver disease. Gut 1986;27(9):1073-90.
28. Skinner RK, Sherlock S, Long RG, Wilis MR. 25-Hydroxylation of vitamin D in primary biliary cirrhosis. Lancet 1977;1(8014):720-1.
29. Plourde V, Gascon-Barre M, Coulombe PA, Vallieres S, Huet PM. Hepatic handling of vitamin D3 in micronodular cirrhosis: a structure-function study in the rat. J Bone Miner Res 1988;3(4):461-71
30. American Gastroenterological Association medical position statement: osteoporosis in hepatic disorders. Gastroenterology 2003;125(3):937-40
31. Ninkovic M, Skingle SJ, Bearcroft PW, Bishop N, Alexander GJ, Compston JE. Incidence of vertebral fractures in the first three months after orthotopic liver transplantation. Eur J Gastroenterol Hepatol 2000;12(8):931-5.
32. Shiomi S, Masaki K, Habu D, Takeda T, Nishiguchi S, Kuroki T, et al. Calcitriol for bone disease in patients with cirrhosis of the liver. J Gastroenterol Hepatol 1999;14(6):547-52.
33. Ebeling PR. Approach to the patient with transplantation-related bone loss. J Clin Endocrinol Metab 2009;94(5):1483-90.

34. Hawkins FG, Leon M, Lopez MB, Valero MA, Larrodera L, Garcia-Garcia I, et al. Bone loss and turnover in patients with liver transplantation. Hepatogastroenterology.1994;41(2):158-61.
35. Crawford BA, Kam C, Pavlovic J, Byth K, Handelsman DJ, Angus PW, et al. Zoledronic acid prevents bone loss after liver transplantation: a randomized, double-blind, placebo-controlled trial. Ann Intern Med 2006;144(4):239-48
36. Shane E RH. Osteoporosis after solid organ or stem cell transplantation. UpToDate. Basow, DS (Ed), UpToDate, Waltham, MA ed; 2009.
37. Cohen A, Ebeling P, Sprague S, and Shane E. Transplantation Osteoporosis. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, sixth edition. American Society of Bone and Mineral Research 2006;56:302.
38. Shiomi S, Masaki K, Habu D, Takeda T, Nishiguchi S, Kuroki T, et al. Calcitriol for bone disease in patients with cirrhosis of the liver. J Gastroenterol Hepatol 1999;14(6):547-52.
39. Hay JE, Malinchoc M, Dickson ER. A controlled trial of calcitonin therapy for the prevention of post-liver transplantation atraumatic fractures in patients with primary biliary cirrhosis and primary sclerosing cholangitis. J Hepatol 2001;34(2):292-8.
40. Valero MA, Loinaz C, Larrodera L, Leon M, Moreno E, Hawkins F. Calcitonin and bisphosphonates treatment in bone loss after liver transplantation. Calcif Tissue Int 1995;57(1):15-9.
41. Riemens SC, Oostdijk A, van Doormaal JJ, Thijn CJ, Drent G, Piers DA, et al. Bone loss after liver transplantation is not prevented by cyclical etidronate, calcium and alphacalcidol. The Liver Transplant Group, Groningen. Osteoporos Int 1996;6(3):213-8.
42. Reeves HL, Francis RM, Manas DM, Hudson M, Day CP. Intravenous bisphosphonate prevents symptomatic osteoporotic vertebral collapse in patients after liver transplantation. Liver Transpl Surg 1998;4(5):404-9.
43. Dodidou P, Bruckner T, Hosch S, Haass M, Klar E, Sauer P, et al. Better late than never? Experience with intravenous pamidronate treatment in patients with low bone mass or fractures following cardiac or liver transplantation. Osteoporos Int 2003;14(1):82-9.
44. Pennisi P, Trombetti A, Giostra E, Mentha G, Rizzoli R, Fiore CE. Pamidronate and osteoporosis prevention in liver transplant recipients. Rheumatol Int 2007;27(3): 251-6.
45. Millonig G, Graziadei IW, Eichler D, Pfeiffer KP, Finkenstedt G, Muehllechner P, et al. Alendronate in combination with calcium and vitamin D prevents bone loss after orthotopic liver transplantation: a prospective single-center study. Liver Transpl 2005;11(8): 960-6.
46. Atamaz F, Hepguler S, Akyildiz M, Karasu Z, Kilic M. Effects of alendronate on bone mineral density and bone metabolic markers in patients with liver transplantation. Osteoporos Int 2006;17(6):942-9.
47. Bodingbauer M, Wekerle T, Pakrah B, Roschger P, Peck-Radosavljevic M, Silberhumer G, et al. Prophylactic bisphosphonate treatment prevents bone fractures after liver transplantation. Am J Transplant 2007;7(7):1763-9.
48. Misof BM, Bodingbauer M, Roschger P, Wekerle T, Pakrah B, Haas M, et al. Short-term effects of high-dose zoledronic acid treatment on bone mineralization density distribution after orthotopic liver transplantation. Calcif Tissue Int 2008;83(3):167-75.

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Differential diagnosis and management of pain associated with multiple vertebral hemangiomas. A case report

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Clinical case

We present a case of a woman of 71 years of age with a history of epilepsy, mixed hyperlipemia, depressive syndrome and established osteoporosis, having had a previous Colles fracture on the left-hand side at the age of 52. She was following treatment with 750 mg/day of valproic acid, 40 mg/day of atorvastatin, 100 mg/day of trazodone, 20 mg/day of omeprazol, 35 mg weekly of risedronate and calcium and vitamin D supplements (550 mg/day of calcium element and 400 UI of vitamin D). For at least the last 10 years she presented with back pain, which improved only partially with rest and on occasion the pain, both dorsal and lumbar, woke her in the night. This pain had increased progressively in intensity such that it interfered with the basic activities of daily life. For this reason she was studied five years previously in another clinic without their arriving at a conclusive diagnosis. Nuclear Magnetic Resonance (NMR) of the spinal column had been carried out in which various lytic lesions were found, suggestive of metastasis in D6-D8. However, after an exhaustive examination, which included bone gammagraphy, computerised axial tomography (CAT), thoraco-abdominal mammography, tumour markers, proteinogram and thyroidal echogram, no primary tumour was found and only analgesic treatment was prescribed. 100 μg/hour every 72 hours of transdermic fentanil, 575 mg (3 cp/day) of metamizol and 300 mg/day of gabapentine was usually used.

She attended our clinic due to an increase in the intensity of these back pains, fundamentally in the last few months, without a clearly associated constitutional syndrome, nor previous trauma, or reduction in spirits. She did not have measurable fever, retained her strength and mobility, was able to walk without support and did not present sensory disturbances of any kind.

In the physical examination there was nothing noteworthy, except for pain on tapping the irradiated middle dorsal processes on the right-hand side, without palpable soft tissue mass. The neurological examination showed everything to be completely normal.

The analyses carried out showed discrete normochromic normocytic anaemia (haemoglobin 10.8 g /dL, haematocrit 31.7%, VCM 91.8 fL) with normal levels in the rest of the haemogram series and a velocity of globular sedimentation (VGS) of 35 mm (the second hour was not needed). The times of coagulation and biochemistry (which included the metabolism of iron, hepatic and lipid profile, proteinogram, thyroid hormones and levels of vitamin B12) were normal. The same was the case with the elemental urine analysis. A Mantoux test and blood tests for *salmonella* and *brucella* were carried out, all tests being negative. Similarly, levels of antistreptolysin-O (ASLO) were less than 200.

The following imaging tests were carried out: 1. An X-ray of the thorax, with no mediastinal pathology apparent, with multiple bibasal pulmonary linear opacities in both pulmonary fields compatible with laminar atelectasis by hyperventilation. In the bone, in the simple spinal X-ray there was an affectation in D6-D7-D8 with a partial collapse of vertebral bodies, and sclerosis, with erosions, of the surfaces of the vertebral end plates. 2. A CAT of the dorso-lumbar spinal column, where a lytic lesion was observed, with a well-defined border, in the right lateral section of the body of D8, with a drop of fat in its interior which suggests the possibility of vertebral hemangioma (Figure 1). There are also other images compatible with vertebral hemangiomas in D12 and L1, specifically, in the right lateral section of the vertebral body, surrounded by sclerosis (Figure 2). Notable is a mass of soft tissues, in the bilateral and pre-vertabral para-spinal space, in the coronal reformatting and in the axial cortex. 3. An NMR, in which were observed multiple hypersignal lesions, affecting essentially vertebrae D5 to D9, as well as D11, and, in the lumbar region, L4 and L5. There was, in turn, a significant affectation on the bodies of D6, D7 and D8, with a low signal in sequences T1, and discrete hypersignal in sequences T2, with minimum increase in the pre-vertebral soft tissues and small right anterolateral epidural cuff, without producing compression in the low dorsal medulla. Also described were hyperintense images in sequences T1 and T2 in the vertebral bodies of L4, L2, D12 and D8 in the right half, which could be related to angiomas and/or lipomas (it was too long and exhaustive). 4. Bone gammagraphy with HDP-Tc-99m, which showed an increased deposit in vertebra D7 to D9, which could be considered as vertebral crushing, and in both sternoclavicular joints. Also found was hyperuptake in L4 and L5, with a possible central cold area in L5. The examination with gallium showed up some physiological activity, without evidence of points of hyper-uptake coinciding with the deposits described in the study with HDP-Tc-99m. In conjunction, the examination resulted in a significant increase in osteoblastic activity in the signalled regions, with neither hyperemia nor accompanying signs of inflammation.

Before the new doubts were raised, regarding a previous diagnosis over five years ago, it was decided to carry out a bone biopsy of the vertebral bodies of L4 and D5. In the anatomo-pathological study enlarged bone trabeculae were observed with many cementation lines. Atypias were not observed. The medullar spaces were occupied by conjunctive tissue which was mostly loose and there were no infiltrators or tumourous cells. A microbiological study of the sample was also carried out (bacilloscopy, specific cultures for bacteria, myobacteria and fungi) which equally gave negative results.

In summary, after the re-evaluation of the case, the overall picture of chronic back pain evolved over a number of years, and crushed vertebrae, were catalogued as multiple vertebral hemangiomatosis, manifested above all by pain due to bone expansion and vertebral collapse.

Once the different therapeutic options were evaluated it was decided to opt for radiotherapy of D8 and D12 with a total dose given of 30Gy. With this the patient developed well, with a reduction in pain and in the dose of analgesia required.

Discussion

Hemangiomas are benign tumours of vascular origin with scarce malignant metaplasia, but occasionally with aggressive behaviour. In reality they are not considered to be a true neoplasia, rather a congenital anomaly originating in the embrionic capture of the mesodermic tissue. These yolk sacs proliferate, giving way to masses which resemble neoplasic tissue.

Vertebral hemangiomas have an incidence of 11% in the general population. They correspond to 1% of the total bone neoplasias, their frequency increasing with age, they are generally diagnosed in adults or older people and are more common in women[1-3].

They are often seen as single localised lesions in a single vertebral body, although they can also extend towards the posterior arch. Less frequently there are cases with an affectation of a number of vertebral bodies. The thoracic region is usually the most affected. Only 0.9-1.2% are symptomatic. Of these, 54% give pain, and 45% have neurological manifestations which could be the medullar and/or radicular compression, generally sub-acute. However, the possibility of growth or extension of a vertebral hemangioma is extremely low, and because of this the tumour seldom break the cortex.

Differential diagnosis, above all in the case of multiple vertebral hemangiomas should be carried out with Paget's disease, bone metastasis, haematological tumours such as myeloma or leukaemia, and other tumours of vascular origin such as hemangioblastoma or hemangioendothelioma. The X-ray images are often diagnostic. However, since there are hemangiomas with different image patterns histological diagnosis is occasionally necessary[2,3].

What stands out in our case is the initial diagnostic direction which was indicated in the first examinations carried out by another clinic. However, in our clinic it was felt that the passing of time, and the lack of data indicating a tumoral process, pointed towards the diagnosis of multiple hemangiomas.

A simple X-ray of a vertebral hemangioma offers an image which depends on the location. In the spinal column a pattern of vertical parallel striations is observed as a characteristic image, like the stripes in a "prison cell", which can resemble a honey comb. They are generally found in the lower thoracic region and do not cause growth in the vertebral body[4].

In the CAT scan the thick bony trabeculae are seen in the images as highly characteristic "spines of bone", CAT being the tool which usually best defines the bone architecture and is the best method of imaging diagnosis[5].

Figure 1. Spinal CAT. Axial Scan at the level of D8 in which is observed a lytic lesion with a well-defined border in the right lateral section of the vertebral body, which contains a drop of fat in its interior which suggests the possibility of vertebral hemangioma

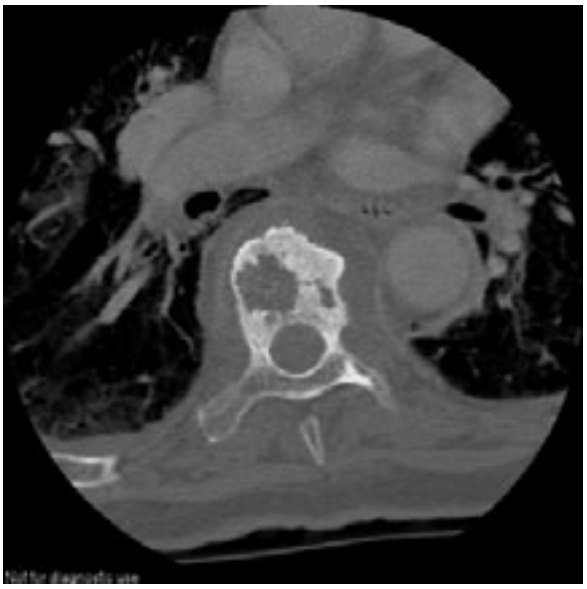
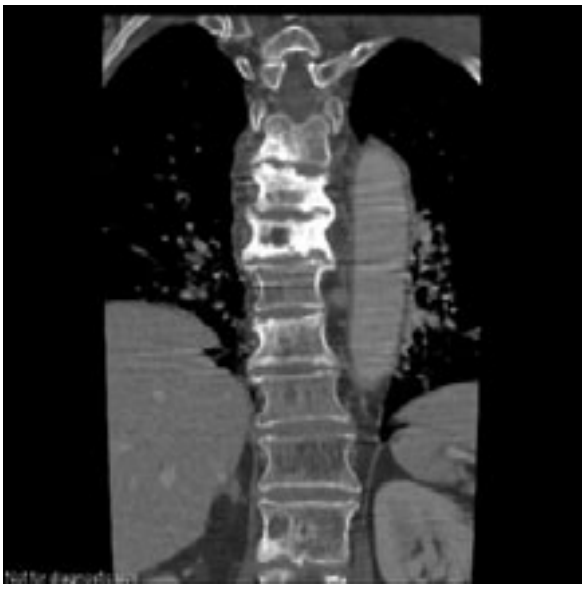


Figure 2. CAT of dorsal spinal column. Coronal reformatting in which are observed lytic lesions with well defined contours, surrounded by sclerosis in many vertebral bodies, essentially in D6-D8, D10 and D13, compatibles with vertebral hemangioma



In the NMR they appear as images of voids or of hyperintensity related to the presence of adipose tissue, blood vessels and oedema. The possibility of changes in the spaces and the adjacent soft tissues when there are partial ruptures with haemorrhaging of these hemtengiomas has been described. These images could suggest differential diagnosis, including vertebral osteomyelitis. NMR is essential in cases in which there is myelopathy since it is possible to image the nervous tissue and the compressive tissue, and in addition it acts as a prognostic study since the isointense images in T1 and the hyperintense images in T2 are associated with hypervascularity and an increase in the potential to medullar compression[6].

The therapeutic options for cases of symptomatic multiple hemangiomas are: radiotherapy, endovascular embolization, infiltration of the vertebral body with ethanol, vertebroplasty or surgical procedures such as decompressive laminectomy and resection of the vertebral body if necessary[7,8].

Embolization is a temporary method of diminishing the risk of haemorrhage, although there is a risk that with the nutritional artery being common with the vertebral artery, a medullar ischemia is provoked[9]. For this reason, an angiograph may help determine the nutritional blood vessels of the hemangioma and with this the viability of carrying out an embolisaion without risk of compromising the medullar circulation.

Vertebroplasty can prevent the collapse of the vertebral body, but not destroy the vascular formations; hemangioma, then, may follow an expansive process with the subsequent neurological symptoms and possible complications (pulmonary embolism, etc.)[10-12].

Fernández et al.[13] evaluated the effects of radiotherapy (20-30Gy) in a group of 7 patients with symptomatic vertebral hemangiomas followed for an average of 19 months and found that the treatment was effective, with no relapse in 6 patients, and what's more, presented no toxic effects. More recently Heyd et al.[14] described 63 cases treated exclusively with radiotherapy (30.0 Gy), in which 57% had a complete remission of symptoms, 32% a partial remission, and in 11% they obtained no response. With this they concluded, equally, that radiotherapy is very useful in the management of the symptoms of these patients, although due to the time required to take effect, in those cases with neurological symptoms (medullar compression) surgical treatment should be indicated first, and subsequently radiotherapy, with the aim of preventing relapse. Although radiotherapy helps to obliterate the hemangiomas and produces an improvement in the painful symptoms, there have been cases described in which it can produce complications such as medullar necrosis or myelitis[15].

The biological mechanisms by which the pain symptoms are seen to be diminished are controversial: they could be due to an anti-inflammatory effect, or to the destruction of the anomalous blood vessels by the phenomenon of vascular fibrosis[1].

In another work, even more recent, the same authors present a more extended and up to date series of cases of vertebral hemangioma treated with radiotherapy (a total of 84 patients with 96 symptomatic lesions). The authors conclude that radiotherapy is an easy, safe and effective method of alleviating the pain associated with these lesions, showing that a total dose of at least 34 Gy was ideal for achieving the most satisfactory response. Among the secondary effects of the treatment were described cutaneous ulcerations and risk of carcinogenesis in 2.4% of patients[1].

Embolization, alcoholisation and vertebroplasty of multiple vertebral hemangiomas are risky, and the absence of neurological compromise discounts surgery as the first choice, for which reason radiotherapy was the treatment opted for. The treatment carried out was effective, bringing a reduction in the dose of analgesics (treatment with strong opiates and gabapentine were successfully withdrawn), with the consequent reduction in possible secondary effects.

In conclusion, we believe that the case described is relevant due to the clinical and radiological presentation (multiple hemangiomatosis), the initial delay and confusion in the diagnosis (which is usually carried out with a radiological examination), as well as for her excellent response to radiotherapy treatment.

Although there are many ways of treating vertebral hemangiomas, there are no guides to its management; there are difficulties in its diagnosis in the asymptomatic phase of the disease, and treatment is generally suggested when there are complications such as fracture or secondary compression. In spite of this, it is necessary to emphasise the importance of a precise diagnosis and an appropriate follow up to avoid severe and permanent consequences.

Bibliography

1. Heyd R, Seegenschmiedt MH, Rades D, Winkler C, Eich HT, Bruns F, et al. German Cooperative Group on Radiotherapy for Bening Diseases: Radiotherapy for Symptomatic Vertebral Hemangiomas: Results of a Multicenter Study and Literature Review. Int J Radiat Oncol Biol Phys 2009 Aug 20. [Epub ahead of print].
2. Pastushyn AI, Slin´Ko EI, Mirzoyeva. Vertebral hemangiomas: diagnosis, management, natural history and clinicalpathological correlates in 86 patients. Surg Neurol 1998;50:535-47.
3. Korres DS, Karachalios T, Roidis N, Bargiotas K, Stamos K. Pain pattern in multiple hemangiomas involving non adjacent levels: report of two cases. Eur Spine J 2000;9:256-60.
4. Alonso G, Reyes García R, Fernández García D, Muñoz Torres M. Hemangioma vertebral. Rev Esp Enf Metab Óseas 2008;17(3):49-50.
5. Rudnick J, Stern M. Symptomatic thoracic vertebral hemangioma: A case report and literature review. Arch Phys Med Rehabil 2004;85:1544-7.
6. Cross JJ, Antoun NM, Laing RJ, Xuereb J. Imaging of compressive vertebral haemangiomas. Eur Radiol 2000;10:997-1002.
7. Acosta FL Jr, Sanai N, Chi JH, Dowd CF, Chin C, Tihan T, et al. Comprehensive management of symptomatic and aggressive vertebral hemangiomas. Neurosurg Clin N Am 2008;19:17-29.
8. Bremnes RM, Hauge HN, Sagsveen R. Radiotherapy in the treatment of symptomatic vertebral hemangiomas: technical case report. Neurosurgery 1996;39:1054-8.
9. Fox MW, Onofrio BM. The natural history and management of symptomatic and symptomatic vertebral hemangiomas. J Neurosurg 1993;78:36-45.
10. Deramond H, Damasson R, Galibert P. Percutaneous vertebroplasty with acrylic cement in the treatment of aggressive spinal angiomas. Rachis 1989;1:143-53.
11. Galibert P, Deramond H. Percutaneous acrylic vertebroplasty as a treatment of vertebral angioma as well as painful and debilitating diseases. Chirurgie 1990;116:326-34.
12. Ide C, Gangi A, Rimelin A, Beaujeux R, Maitrot D, Buchheit F. Vertebral hemangiomas with spinal cord compression: the place of preoperative percutaneous vertebroplasty with methyl methacrylate. Neuroradiology 1996;38:585-9.
13. Fernández F, Moreno A, Quiles JC, Yacer C, Andreu FJ. Hemangiomas vertebrales. Historia natural, diagnóstico y tratamiento. Papel de la radioterapia. Clin Transl Oncol 2001;3:151-4.
14. Heyd R, Strassmann G, Filipowicz I, Borowsky K, Martin T, Zamboglou N. Radiotherapy in vertebral hemangioma. Rontgenpraxis 2001;53:208-20.
15. Guedea F, Majo J, Guardia E, Canals E, Craven-Bartle J. The role of radiation therapy in vertebral hemangiomas without neurologic signs. Int Orthop 1994;118:77-9.

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Tomographic pattern of bone permeability suggestive of secondary osteoporosis

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Introduction

OP is a generalised disease of the skeleton characterised by low bone mass and an alteration in bone micro-architecture, with an increase in its fragility and consequently, a greater tendency to fracture[1]. Primary OP is that in which the reduction in bone mass can be explained by the changes brought about by aging, such as the hormonal changes produced in the menopause; the concept of secondary OP is reserved for that which can be caused or exacerbated by other pathologies or medications[2]. The prevalence of secondary OP is highly variable, depending on age, sex, racial group, etc. In addition, it is not always possible to talk of an isolated cause as the origin of many cases of osteoporosis, rather, a multifactorial etiology is quite frequently found. Thus, while the prevalence of cases of secondary OP in males reaches 64%[3], in perimenopausal women the prevalence is around 50%, diminishing after the menopause to a not insignificant level of 20 to 30%[2].

OP is a multifactorial disease to whose genesis contribute numerous genetic and environmental factors; each factor carries a relatively small weight in the development of the disease, with the exception of ageing and the menopause. The causes of secondary OP are multiple, from genetic, endocrinal, gastrointestinal and haemetologicial diseases, to nutritional and pharmacological factors.

Although the diagnosis of OP is established through densitometric criteria, supported on occasions by clinical criteria[4], there are alterations in other imaging tests –conventional X-ray, computerised tomography (CT) and magnetic resonance (MR)– which should make us suspect this diagnosis. Thus, many cases of OP may be suspected in a casual way through an X-ray examination for another reason, or in subjects with fractures and risk factors for the disease.

The fact which drives the publication of this clinical case in our environment is based on three fundamental aspects: 1) the importance of specific X-ray examinations distinct from bone densitometry in the diagnosis of OP, 2) a review, in practical terms, of the epidemiology of secondary OP and 3) the necessity of maintaining clinical suspicion in selected patients, with negative results in the usual screening tests, which allow us to establish an early diagnosis of potentially curable diseases whose late diagnosis can result in high morbimortiality.

Clinical case

A male patient of 46 years of age, allergic to penicillin and roxithromycin, businessman by profession, sedentary for a large part of his working day. Began two months before the start of the study with pain in the lower dorsal region, mechanical in character, radiating towards the abdominal region, which was treated with analgesia and muscle relaxants, with partial improvement. Months before he had suffered an accidental trauma of moderate intensity in the right costal zone, with intense, stabbing pain which reduced on its own in a few weeks.

Figure 1. MR of dorso-lumbar spinal column. Vertebral wedging anterior to D7

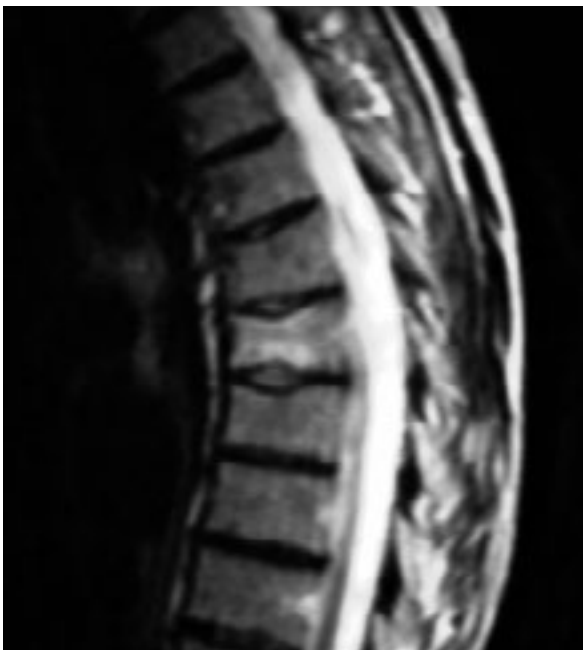
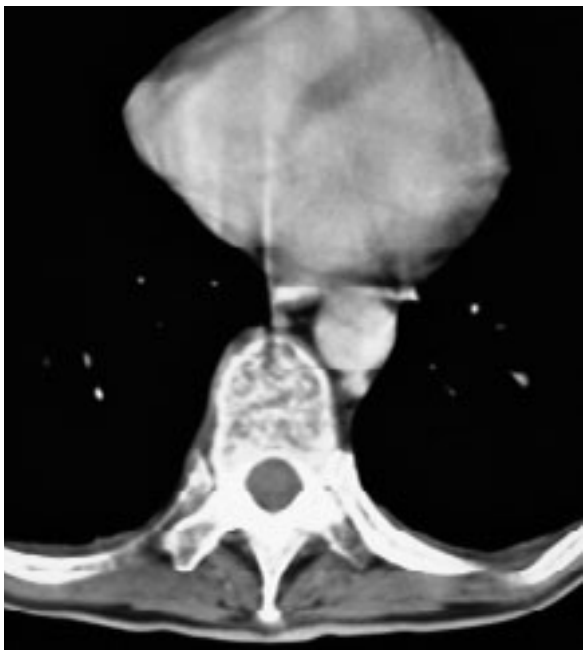


Figure 2. Thoracic CT. Vertebral permeative bone pattern



Physical examination

The patient presented in a generally good state, without any neurological symptoms, good hydration and cutaneo-mucous perfusion, eupneic at rest, with blood pressure of 140/70 mmHg and a cardiac rate of 80 lpm, afrebrile, weight of 60 kg, height of 180 cm, BMI 19 kg/cm^2. The cervical region was normal. The cardiac tones were rhythmic, without murmurs and the breath sound was conserved. Without alterations in the abdominal examination and in the four limbs. Discrete dorsal kyphosis, with pain when the right lower paravertebral musculature was palped. The Lassegue manoeuvre was negative. The external genitals and secondary sexual characteristics were normal. He adopted an antalgic posture.

Complementary examinations

The haemogram presented haemoglobin of 11.2 g/dL (normal values 13-18), haematocrit 31.9% (normal values 39-54%), average corpuscular volume 93.5 fL (normal values 80-99), with platelets and white blood cells within normal levels. The velocity of globular sedimentation was normal. Notable in the biochemistry were urate at 7.2 mg/dL (normal values 3,4-7), phosphate 4.6 mg/dL (normal values 2.7-4.5), alanine aminotransferase 45 UI/L (normal values 2-41), with the values of renal function, thyroid hormones, parathyroid hormone, folic acid, vitamin B12, ferric parameters, lipid profile, hepatic profile, lactate dehydrogenase, proteins, calcium, C reactive protein, cortisol and testosterone, being normal. The coagulation study was normal, as was the urinary ion excretion. The serology for brucella and the urinary bacilloscopy were negative. The markers for digestive, pulmonary and prostate tumours were normal. The immunochemical study showed hypogammaglobulinemia with IgG values of 335 mg/dL (normal values 700-1,600), IgA of 119 mg/dL (normal values 70-400), IgM of 5 mg/dL (normal values 40-230). The Mantoux intradermoreaction was negative when taken at 48 and 72 hours. In the simple X-ray of the dorsolumbar spinal column a mild wedging of the vertebral body of D7 was observed. The dorsal MR scan showed a wedging below D7 which fundamentally affected the superior epiphysary platform, without affectation of the posterior wall or the adjacent mass of soft tissues (Figure 1). The bone gammagraphy showed a reinforced trace capture in the D7 area, compatible with vertebral crushing. The thoraci-abdominal-pelvic CT scan did not show changes in any solid organs, or adenopathies in any of the lymphatic chains studied. However, there was permeative bone pattern in practically all the bones, with some images of endocystic scalloped bleeding, including some with rupture of the cortex (Figure 2).

In the face of the bone findings and keeping a high level of clinical suspicion, despite the absence of monoclonal hypergammaglobulinemia, an aspiration of the bone medulla was requested which was cytologically compatible with monoclonal gammopathy of type multiple myeloma (MM). The urinary immunofixation detected *kappa* type Bence Jones protein. With the diagnosis of *kappa* type Bence-Jones MM, stage IIIB, poly-chemotherapeutic treatment was initiated according to the VAD (vincristine, adriamycin and

Table 1. Causes of secondary osteoporosis

Hypogonadal states	Endocrine disorders	Gastrointestinal diseases
-Insensitivity to androgens -Eating disorders -Amenorrhea in female athletes -Hyperprolactinemia -Panhypopituitarism -Early menopause -Turner & Klinefelter syndrome	-Acromegaly -Suprarrenal deficiency -Cushing's disease -Diabetes mellitus type I -Hyperparathyroidism -Tumoral secretion of PTH -Hyperthyroidism -Nutritional deficiency in Ca, Mg, vit D.	-Coeliac disease -Gastrectomy -Malabsorption -Inflammatory intestinal disease -Primary bilial cirrhosis -Serious hepatic disease -Pancreatic exocrine deficiency
Genetic disorders	**Haematological disorders**	**Drugs**
-Haemochromatosis -Hypophosphatasia -Osteogenesis imperfecta -Ehler-Danlos syndrome -Marfan syndrome	-Multiple myeloma -Leukemias and lymphomas -Systemic mastocytoses -Pernicious anaemia	-Anticoagulants: heparins and dicumarinics -Anticomitials -Cyclosporin and tacrolimus -Cytotoxic drugs -Glucocorticoids and ACTH -Methotrexate
Rheumatic diseases	**Organ transplants**	
-Rheumatoid arthtritis -Ankylosing spondylitis	-Bone marrow transplant -Kidney, liver, lung or heart transplant	

dexamethasone) protocol, together with zoledronic acid, over 4 cycles, with a partial response. The fitting of an orthopaedic corset was required to fix the dorsal lesion, as well as kinesitherapy exercises. Subsequently a self-transplant of peripheral blood progenitor cells as a consolidation treatment, and because he had an HLA-identical brother, an allogenic transplant was carried out, with a very good response, with the patient now being in complete remission after a three year follow up.

Discussion

Multiple myeloma (MM) is a neoplasia of B cells characterised by an uncontrolled accumulation of clonal plasmatic cells in the bone medulla combined with the production of monoclonal immunoglobulin detectable in blood or urine. Clinically it is manifested by signs and symptoms resulting from organic affectation, such as anaemia due to medullar deficiency, immune dysfunction with recurrent infections, skeletal lesions with hypercalcemia and renal affectation[5-10]. The bone lesions can take various patterns, with the most common being multiple osteolitic lesions, and much less frequently the development of diffuse osteopenia[11], both due to an increase in osteoclast activity.

MM is present principally in subjects over 50 years of age (only 15% in those younger than 50), with a median incidence at 65 years of age, without differences between the sexes, and being more frequent in black people[6]. In our case, neither the epidemiological data nor the initial analytical values were compatible with the initial diagnosis of MM. The absence of anaemia, hypercalcemia, renal deficiency or hypergammaglobulinemia, typical in MM, combined with an anodyne clinical picture, can reinforce the direction our diagnosis towards other more probable pathologies. Only the maintenance of a strong clinical suspicion in patients low intensity fractures and tomographic pattern of bone permeability, although other factors may be present for low bone mass or increased risk of fracture, can bring a correct diagnosis.

The bone lesions in MM are due to an asynchronicity between the formation and destruction of bone, and here the increase in the activity of the osteoclasts is not found to be balanced by a comparable level of bone formation activity[12,13]. The myelomatous cells stimulate the formation and activation of the osteoclasts, due to the interaction which occurs between the receptor for the activation of nuclear factor kB (RANK) on the surface of the osteoclast and the ligand RANKL existing in the stromal cells of the bone medulla. The myelomatous cells increase the expression of RANKL, by a cell-to-cell contact mechanism[14,15]. The RANK-RANKL signal is normally counteracted by osteoprotegerin, which is reduced by the direct action of the myelomatous cells[16]. In addition, there is, in advanced stages of bone disease, resistance in the myelomatous cells to some chemotherapies, which could be due in part to the same interaction with the osteoclasts[17,18].

The biphosphonates are an essential component in the treatment of MM, since they reduce skeletal morbidity. In Europe only clodronate, pamidronate and zoledronate are approved for patients with MM and osteolitic lesions. The choi-

ce between them essentially depends on the way they are administered and the patient's concomitant treatment. Both pamidronate and zoledronate are equally effective and their use is intravenous, with the latter requiring less time for infusion. Zoledronate has shown the capacity to prevent the development of osteolitic lesions and to reduce the mass of bone tumours in patients with MM, as well as reducing the number of bone fractures in patients with OP[19].

OP has been traditionally considered a women's disease, but today it is known to have great importance to the male sex. In males OP appears later, due to their higher peak in bone mass in youth, and the lower loss of bone mass, lacking such a marked period of bone loss as the menopause in women, for which reason the complications arising from osteoporosis occur much later than in women. OP, cause of the crushing-fracture of the vertebra, differs in its etiology between the sexes. While in post-menopausal women, 70-75% of cases are due to the menopause itself, in males secondary forms constitute up to 50% of cases. The rest of the male forms of this syndrome are catalogued as idiopathic[18,20]. The three most important causes of osteoporosis in males are alcoholism, excess of glucocorticoids (both in Cushing's syndrome and in chronic steroid treatment) and hypogonadism[18], although a long list of secondary causes of OP (Table 1) should also be taken into account. The search for a gastrointestinal malabsorptive pathology must be prioritised, when we do not find the causal process for OP.

In males from 70 years of age, due to the loss of bone mass associated with age, we consider OP to be explained by the aging process, without focussing on the search for secondary causes[20]. However, we found males below 70 with this type of OP and others of a greater age in whom the clinical suspicion results in us focussing on the search for secondary causes or OP.

In conclusion, the causes of OP are multiple, more, even, in males, which includes aging itself. For this reason it is necessary always to maintain a high level of clinical suspicion, in spite of little specific clinical data, to be able to arrive at a correct diagnosis of the underlying disease, thus diminishing the morbimortality of the patient.

Bibliography

1. NIH consensos panel: Consensus development conference: diagnosis, prophylaxis and treatment of osteoporosis. Am J Med 1993,94:646-50.
2. Stein E, Shane E. Secondary osteoporosis. Endocrinol Metab Clin N Am 2003;32:115-34.
3. Harper KD, Weber TJ. Secondary osteoporosis: diagnostic considerations. Endocrinol Metab Clin N Am 1998;27:325-48.
4. Kanis JA. Diagnosis of osteoporosis and assessment of fracture risk. Lancet 2002;359:1929-36.
5. Kyle RA, Rajkumar SV. Multiple myeloma [published correction appears in N Engl J Med. 2005;352:1163]. N Engl J Med 2004;351:1860-73.
6. Kyle RA, Gertz MA, Witzing TE, Lust JA, Lacy MQ, Dispenzieri A, et al. Review of 1207 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33.
7. International Myeloma working Group: Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003;121:749-57.
8. Rajkumar SV, Dispenzieri A, Fonseca R, Lacy MQ, Geyer S, Lust JA, et al. Thalidomide for the previously untreated indolente or smoldering multiple myeloma. Leukemia 2001;15:1274-6.
9. Rajkumar SV, Greipp PR. Prognostic factors in multiple myeloma. Hematol Oncol Clin North Am 1999;13:1295-314.
10. Smith A, Wisloff F, Samson D. Guidelines on the diagnosis and Management of multiple myeloma 2005. Br J Haematol 2005;132:410-51.
11. Mundy GR. Myeloma bone disease. Eur J Cancer 1998;34:246-51.
12. Hjertener O, Standal T, Borset M, Sundan A, Waage A. Bone disease in multiple myeloma. Medical Oncology 2005;23:431-41.
13. Berenson JR. Myeloma bone disease. Best Pract Res Clin Haematol 2005;18:653-72.
14. Pearse RN, Sordillo EM, Yaccoby S, Wong BR, Liau DF, Colman N, et al. Multiple myeloma disrupts the TRANCE/osteoprotegerin cytokine axis to trigger bone destruction and promote tumor progression. Proc Natl Acad Sci USA 2001 Sep 25;98:11581-6.
15. Giuliani N, Bataille R, Mancini C, Lazzaretti M, Barillé S. Myeloma cells induce imbalance in the osteoprotegerin/osteoprotegerin ligand system in the human bone marrow environment. Blood 2001 Dec 15;98:3527-33.
16. Toshio Matsumoto and Masahiro Abe. BoneKEy-Osteovision 2006;3:8-14.
17. Abe M, Hiura K, Wilde J, Shioyasono A, Moriyama K, Hashimoto T, et al. Osteoclasts enhance myeloma cell growth and survival via cell-cell contact: a vicious cycle between bone destruction and myeloma expansion. Blood 2004;104:2484-91.
18. Bilezikian JP. Osteoporosis in men. J Clin Endocrinol Metab 1999;84:3431-4.
19. E. Terpos, O. Sezer, P.I. Croucher, García-Sanz R, Boccadoro M, San Miguel J, et al. The use of bisphosphonates in multiple myeloma: recommendations of an expert panel on behalf of the European Myeloma Network. Ann Oncol 2009;20:1303-17.
20. Burgess E, Nanes MS. Osteoporosis in men: pathophysiology, evaluation and therapy. Curr Opin Rheumatol 2002;14:421-8.

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Role of calcium and vitamin D in the treatment of osteoporosis

Summary
Our objective has been to develop a position document on the role of calcium and vitamin D in the treatment of osteoporosis, identifying and assessing the grade of evidence which supports the recommendations.
To achieve this aim, the published studies on aspects of pharmacokinetics of calcium, and the usefulness of calcium and vitamin D in the reduction of risk of fragility-related fracture, given on its own, as well as, more commonly used in combination with other drugs, have been reviewed, developing through their analysis, the current recommendations. These have been produced through a pre-specified and reproducible process, which included an accepted model for the evaluation and citing of evidence which supports them. The document, once drafted by the co-ordinators, was reviewed and discussed by all the panel members, to produce the definitive recommendations.
Calcium and vitamin D in themselves have shown their usefulness in the reduction of risk of both vertebral fracture, and hip and non-vertebral fracture. Administered in combination with different drugs they also reduce the risk of new osteoporotic fractures. All treatments indicated for osteoporosis should be administered with a supplement of calcium and vitamin D. To ensure optimum absorption, the calcium and vitamin D should be administered in small doses throughout the day. The calcium salt most used is calcium carbonate, of which there has been the greatest experience, it being, also, the cheapest. Calcium carbonate should be administered with meals for the best absorption. There are no pivotal studies with drugs used for the treatment of osteoporosis carried out with other salts of calcium. Calcium carbonate slightly increases the risk of urolitiasis. Calcium citrate is indicated in those patients with achlorhydia and reduces the risk of urolitiasis, being indicated as the drug of first choice for these patients.

1. Introduction

Osteoporosis. Its importance and the objetives in its treatment

Osteoporosis is the most frequent metabolic bone disease in humans. It was initially defined by Fuller Allbright as "too little bone". Nowadays, the definition accepted by consensus is "systematic skeletal disease characterised by low bone mass and deterioration in the micro-architecture of the bone tissue, with the consequent increase in bone fragility and susceptibility to fractures"[1]. The essential elements of this definition are the low bone mass and the alteration of the micro-architecture, which distinguishes osteoporosis from other bone diseases. The alterations in micro-architecture are characterised by the loss, thinning and lack of connection between the bone trabeculae, the geometry of the bone itself, etc., which have been grouped under the concept of bone quality[2]. All these factors produce a deterioration in the structural integrity of bone and contribute to bone fragility, which brings with it an increased risk of fractures. In fact, fractures and their complications are the clinical manifestations of osteoporosis[3,4]. Considered typically osteoporotic are fractures of the proximal extremities of the femur, vertebra and wrist[5], although, in general, any bone is susceptible to fracture.

Treatment of osteoporosis. Objectives

The principal objective in the treatment of osteoporosis has to be to avoid or reduce the appearance of osteoporotic fractures (whether the first time or with the existence of previous fractures), given that these constitute its principle complication and clinical problem[4-6]. Other objectives, such as the increase in bone mineral density, the modification of the biochemical markers for remodelled bone, or complications and adverse affects, are secondary.

One should also avoid the idea that the treatment of osteoporosis consists solely of the long term administration of a drug which reduces the risk of fractures. The correct treatment indicated requires, in addition, a series of non-pharmacological, but equally important actions, such as abandoning toxic behaviours like tobacco and alcohol abuse, taking daily physical exercise, in accordance with the clinical state of the patient, and having a balanced diet[7,8].

Evidence-Based Medicine (EBM) and drugs used for osteoporosis

At present a wide variety of drugs for the treatment of osteoporosis are available. The greatest number of these have shown their effectiveness through clinical trials carried out in accordance with EBM[9-14], and are thus indicated for the treatment of osteoporosis in both the United States and the European Union.

Nowadays, the studies of drugs for the treatment of osteoporosis are carried out with the principal objectives of the reduction of risk of fracture, since this constitutes the fundamental clinical complication of osteoporosis, and the reason for its importance. From a practical point of view, there is a tendency to separate the reduction in risk of vertebral fracture from that of other fractures, which have been grouped empirically as non-vertebral fractures, which is the term generally used[15,16], given that, as non-vertebral fractures are grouped very different fractures, as much from the point of view of their symptomology as their mortality, such as, for example fractures of the rib and hip. In the past, studies were carried out with the principal objective being to evaluate changes in bone mineral density (BMD). Now, although these are still carried out, their practical usefulness is much less, since it has been observed repeatedly that there is no correlation between increases in BMD and decreased risk of fracture[17,18]. Thus, with such small increases in BMD, such as 5.4%, a decrease in the risk of fracture of 41% has been observed in the case of risedronate[19,20]. Also, in the PROOF study, carried out on calcitonin[21], a reduction in risk of fracture was observed in spite of no changes in BDM being observed. These findings bring to light the important role played by what is now called bone quality, as much in the physiopathology of osteoporosis as in bone resistance[2,5,22].

It is also a rule that patients should be randomly assigned to a treatment or control group, in such a rigorous way that it is subsequently confirmed that there are no statistically significant differences between the groups in their baseline characteristics, with the single exception being the treatment received by one or the other. Thus, the differences subsequently observed can be attributed to the drug. However, although methodologically impeccable, in this type of study the patients in the control group (who, equally to the cases, presented a high risk of suffering fractures) received, up 'til now, only calcium and vitamin D, as well as the placebo. This has provoked an interesting debate from an ethical point of view[23-35].

Another important matter, essential for studies of osteoporosis, is that the sample size should be large. Gone are the days when conclusions were taken on the basis of studies carried out with a few dozen patients. Nowadays, such work is carried out with sample sizes of some thousands of patients. This, on the one hand has the advantage of offering much more solid statistical rigor, but on the other hand, brings the inconvenience of a significantly more costly project proposal, in which, in practice, all studies have to be multi-centred. When databases with this number of patients are handled, it is possible to carry out robust statistical studies, which reach unequivocal conclusions, and, in addition, allow the study of specific subpopulations which begin to reach a respectable size, and to carry out post-hoc analyses.

The studies are usually carried out with a duration of approximately 3 years. When the follow-up is extended for a longer period there is usually a significant number of cases lost, and the final sample size cane become so reduced that it becomes difficult to evaluate the results.

Table 1 shows the criteria proposed by the Centre for Evidence-Based Medicine (CEBM) in Oxford, with hierarchical scales of evidence, from which are established recommendations with respect to the adoption of a specific medical procedure or health intervention, as well as an economic evaluation[10,26-29]. These are available at http://www. cebm.net/levels_of_evidence.asp, and are kept continually updated.

2. Material and methods

This position document has been produced following the criteria of the Working Group of Evidence-Based Medicine for the development of Guides to Clinical Practice[10,11,13,26-28,30,31], as well as the criteria proposed by the Centre for Evidence-Based Medicine (CEBM) of Oxford, with scales for hierarchical classification of evidence, from which have been established recommendations with respect to the adoption of a specific medical procedure or health intervention, as well as an economic evaluation[32-38] (Table 1).

The content of this position document has been developed in the following stages:

a) Meeting of a group of experts on osteoporosis to raise the relevant clinical questions (Table 2).

b) Creation of a systematic review team, formed of two experts in bone mineral metabolism to carry out the search, standard review, critical analysis and tabulation of relevant articles which were published in Castilian and in English from January 1980 to May 2008. The search was carried out using the MeSH terms (Medical Subject Headings) of the National Library of Medicine of National Institutes of Health – (US), related to the theme. With these terms, the following databases were consulted: PubMed, Medline Plus, Cochrane Library, Up to Date and Ovid. Similarly, an ascending search was made of the clinical practice guides previously published on the theme, and articles suggested by the group of experts[11,12,39-43].

c) The articles with the highest level of evidence available for each question asked were included. The works were classified and scored by two independent evaluators on the basis of the criteria previously described. In the case of disagreement, the decision was submitted to the committee of experts.

d) Subsequently, according to the results obtained in the search and classification of the available evidence, a draft of the position document was produced by the group of clinical experts to respond to the questions previously formulated and to agree the recommendations, taking into account social, economic and health repercussions. In the case of disagreements a majority opinion was formed, making clear the lack of unanimity.

3. Results

3.1. Calcium and vitamin D

We had available various studies which compared the reduction in risk of fracture when only calcium and vitamin D were used, with the control group receiving absolutely nothing, taking a true placebo. Although there are various published

Table 1. Level of evidence. CEBM Oxford

Level of evidence	Type of study
1a	Systematic review of randomised clinical trials, with homogeneity
1b	Randomised clinical trial with narrow confidence interval
1c	Clinical practice ("all or nothing") (*)
2a	Systematic review of cohort studies, with homogeneity
2b	Cohort study or randomised clinical trial of low quality (**)
2c	"Outcomes research" (1), ecological studies
3a	Systematic reviews of case-control studies, with homogeneity
3b	Case-control study
4	Series of cases or studies of cohorts or case-control studies of low quality (2)
5	Opinion of experts without explicit critical validation, or based on physiology, "bench research" or "first principles" (3)

A minus sign (-) should be added to indicate that the level of evidence is not conclusive if:
- it is a randomised clinical trial with a broad confidence interval and not statistically significant.
- it is a systematic review with statistically significant heterogenaeity.
(*) Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
(**) For example, with a follow up lower than 80%.
(1) The term "outcomes research" makes reference to cohort studies of patients with the same diagnosis which relate the events which happen to them to the therapeutic measures they receive.
(2) Cohort study: without clear definition of the comparative groups, and/or without objective measurement of the exposures and events (preferably blind), and/or without identifying or controlling adequately known as being variables that may lead to confusion, and/or without complete or sufficiently prolonged follow up. Case-control study: without clear definition of the groups compared, and/or without objective measurement of the exposures and events (preferably blind), and/or without identifying or controlling adequately the known confusing variables.
(3)The term "first principles" makes reference to the adoption of specific clinical practice based on physiopathological principals.

Table 2. Questions produced by the panel of experts

1. Do calcium and vitamin D supplements, in themselves, reduce the risk of fragility-related fractures?
2. Are calcium and vitamin D supplements indicated with other pharmacological treatments for postmenopausal osteoporosis?
3. How many calcium salts are used in the treat ments of osteoporosis and how much calcium element does each contain?
4. Is there a difference in the absorption of calcium between the different salts?
5. What would be the ideal model for the administration of calcium?

works which confirm these findings, we preferred to refer ourselves to the meta-analyses (Table 3) because this type of study has the maximum level in the hierarchy of evidence established by the Centre for Evidence-Based Medicine in Oxford (CEBM). Thus, Bischoff-Ferrarri et al.[44], published a meta-analysis in JAM in 2005 in which they analyse the effect of calcium and vitamin D in the prevention of hip and non-vertebral fractures. The period of review covered from 1960 to 2005, and in the end they were able to include 5 studies of hip fracture which were carried out with a total of 9294 patients, and 7 studies of non-vertebral fractures which included 9820 patients. The authors observed that at a dose of 700-800 UI/day of vitamin D, the reduction in risk of fracture of the hip was 26% (relative risk, RR:0.74; IC 95%: 0.61-0.88) and for non-vertebral fractures, 23% (RR: 0.77; IC 95%: 0.68-0.87), whilst with lower doses of vitamin D, below 400 UI/day, no protection against fracture was observed [Level of evidence 1a].

Subsequently, Boonen et al.[45] deepened the earlier meta-analysis of Bischoff-Ferrari and found that in 4 randomised clinical studies which included 9083 patients, the relative risk of fracture of the hip was not statistically significant (RR: 1.10; IC 95%: 0.89-1.36). Whereas, in the 6 randomised studies in which calcium and vitamin D was administered, which included 45509 patients, the risk of fracture of the hip was reduced by 18% (RR: 0.82; IC 95%: 0.71-0.94). There was no heterogeneity observed among the studies, and an adjusted indirect comparison of the combination of relative risks of both meta-analyses obtained a reduction in the risk of fracture of 25% in patients having received calcium and vitamin D as opposed to those only having received vitamin D (RR: 0.75; IC 95%: 0.58-0.96) [Level of evidence 1a].

More recently, Tang et al.[46], carried out another meta-analysis, using 29 randomised studies which included a total of 63897 patients, analysing both the reduction in relative risk of all fractures, and the increase in bone mineral density. Studying publications in which the principal objectives were the reduction in risk of fracture, they obtained 17 studies which included a total of 52625 patients. In these were found a reduction of 12% in the risk of suffering new fractures due to fragility (RR: 0.88: IC 95%: 0.83-0.95; p= 0.0004). They concluded that the evidence supported the use of calcium, or calcium combined with a vitamin D supplement, in the treatment of osteoporosis in people of 50 or more years of age, and for a maximum therapeutic effect, a dose of 1,200 mg/day of calcium and 800UI/day of vitamin D was necessary [Level of evidence 1a].

On the other hand, vitamin D supplements reduce the risk of falls, which indirectly influences the risk of fracture. Thus, in a meta-analysis published by Bischoff-Ferrari et al.[47] based on 5 randomised clinical studies in which 1237 patients were included, it was observed that vitamin D corrected the risk of falls by 22% (adjusted OR: 0.78; IC 95%: 0.64-0.92) compared with patients who had received only calcium or placebo [Level of evidence 1a].

3.2. Calcium and Vitamin D with anabolic drugs

We referred for each drug to the most representative or pivotal study, the study usually used by the pharmaceutical industry to obtain approval for the treatment of osteoporosis, both in the Untied States and in the European Union.

Among the anabolic drugs, PTH 1-34, or teriparatide, showed its capacity to reduce the appearance of new vertebral fractures in a study carried out in 1637 postmenopausal women with at least one vertebral fracture, and who were randomly assigned to one of three of the following groups for treatment: PTH 1-34 (20 μg or 40 μg), or placebo, daily, subcutaneously, for 3 years. In all these cases 1000 mg daily of calcium and 400-1200 UI/day of vitamin D were also administered. A reduction of 65% in the relative risk of suffering new vertebral fractures was observed in those women who received 20 μg of teriparatide, compared with the placebo group (RR: 0.35; IC 95%: 0.22-0.55), and of 69% in the group which received 40 μg, as against the placebo group (RR: 0.31; IC 95% 0.19-0.50)[48] [Level of evidence 1b].

Another study called TOP (Treatment of Osteoporosis with PTH), was carried out with the intact molecule of PTH (1-84), in which a reduction in the risk of vertebral fracture was shown. Carried out in 2532 women with postmenopausal osteoporosis, it consisted, the same as the earlier studies, of a double blind randomised trial controlled by placebo. The patients were assigned to one of two following treatment groups: PTH (1-84) 100 μg/day, or placebo, subcutaneously. The study lasted 18 months. Once more, all patients in the study were given 700 mg daily of calcium citrate and 400 UI of vitamin D. A reduction of 61% in the risk of new vertebral fractures was obtained in the women in the group who received intact PTH compared with the control group. The relative risk was 0.42 (IC 95%: 0.24-0.72; p< 0.001)[49] [Level of evidence 1b].

Table 3. Meta-analysis which analyses the effect of vitamin D and calcium, alone or together, on the risk of fracture

Meta-analysis first author (Citation)	Year	Nº of studies analysed	Group treated	Drug analysed	% reduction in risk of Fx	Value of p
Bischoff-Ferrari (44)	2005	5 (Hip Fx) 7 (NV Fx)	> 60 years	Vitamin D vs calcium or placebo	> 700-800 UI/day: Hip Fx: 26% NV Fx: 23%	---
Boonen (45)	2007	10 (Hip Fx)	Postmenopausal women and/or men > 50 years	Vitamin D, with or without calcium	Vitamin D + calcium: Hip Fx: 18%	p= 0.0005
Tang (46)	2007	29 randomised	Men and women > 50 years	Calcium, with or without vitamin D	12%	p= 0.0004

Fx: fracture; NV: non-vertebral

3.3. Calcium and vitamin D with anti-resorptive drugs

Etidronate was used by Storm et al. in a study published in 1990 and carried out in 66 postmenopausal women, in which the group which received the etidronate took it at a rate of 400 mg daily for 14 days, with a 13 week break, followed by a repeat of the cycle. The group which received etidronate and the placebo group both received a supplement of calcium and vitamin D. The study lasted 150 weeks (3.1 years) and obtained a statistically significant reduction in the appearance of new vertebral fractures ($p< 0.02$)[50] [Level of evidence 1b].

Alendronate. The FIT (Fracture Intervention Trial) study, randomised double blind placebo-controlled, was designed to observe the effect of alendronate on the incidence of vertebral and non-vertebral fractures in postmenopausal women with low bone mass. The research involved 6459 postmenopausal women with bone mineral density (BDM) in the femoral neck 0.68 g/cm^2 (a T-score equivalent to -1.6 approximately), who were distributed in two branches of the study: in one, those women with vertebral fracture at the baseline; and in the other group, the women with no such fracture. The study of the first branch was carried out in 2027 postmenopausal women with a least one vertebral fracture, who were assigned randomly to one of the two following groups for treatment: alendronate at 5 mg/day, or placebo. The dose of alendronate was increased in the first group to 10 mg/day at 24 months from the start of the treatment. Complementary treatment with calcium carbonate (500 mg of the element calcium) and vitamin D (250 UI) was given daily to those women who had a diet low in calcium (< 1,000 mg/day), who made up 82% of the participants in the study. At the end of the three years they were tracked 2.3% of the women who took alendronate suffered a new clinical vertebral fracture, as opposed to 5% of the women taking the placebo, the relative risk being equal to 0.45 (IC 95%: 0.27-0.72). That is to say, the risk of suffering a new vertebral fracture is reduced to almost half in the patients treated with alendronate at the end of 3 years. The second branch of the study was carried out in 4432 women with low bone mass but without vertebral fracture, with random assignment to the two same treatment groups as with the previous branch (with an equal increase in the dose of alendronate at 24 months and equal conditions of calcium and vitamin D supplements). The results show that the risk of suffering a first vertebral fracture were significantly less in those treated with alendronate, with a reduction of 44% ($p< 0.002$)[51] [Level of evidence].

Risedronate. The pivotal study for risedronate is named VERT (Vertebral Efficacy with Risedronate Treatment). This randomised, double blind, placebo-controlled study, also consisted of two branches, one north American (NA) and the other European-Australian (EA). In the first study 2458 postmenopausal women, younger than 85 and with either at least two vertebral fractures or one vertebral fracture and a low bone mass (T-score < -2), were included. Each patient was assigned to receive one of the following treatments: a) risedronate at 2.5 mg/day; b) risedronate at 5 mg/day; and c) a placebo. All the women received a supplement of calcium carbonate (1000 mg/day) in a single dose at lunch or dinner, and those who presented low levels of 25 (OH) vit D (< 16 ng/ml or 40 nmol/l) received vitamin D (500 UI). The group which received 2.5 mg of risedronate left the study after a year due to a protocol correction. At 3 years there was a significant reduction in the relative risk of morphometric vertebral fracture of 41% (IC 95%: 18-58%; p= 0.003) in patients treated with 5 mg of risedronate with respect to the placebo group, and already in the first year a reduction of 65% (IC 95%: 38-81%) was seen, also significant ($p< 0.001$). The accumulated incidence of non-vertebral fractures at 3 years was 39% less in the group treated with risedronate (IC 95% 6-61), a significant figure (p= 0.02).

In the European-Australian branch 1226 postmenopausal women were recruited with at least two vertebral fractures. The treatment groups were equal, including the calcium and vitamin D supplements, as well as the duration of the study. The group on 2.5 mg of risedronate abandoned the trial after 2 years. The reduction in the risk of incidence of vertebral fracture was 49% with risedronate at 5 mg as opposed to the placebo after 3 years of treatment (p< 0.001). A reduction of risk with risedronate was also seen during the first year, being 61% (p= 0.001). The risk of non-vertebral fractures was reduced by 33% compared with the control group at 3 years (p= 0.06)[52,53] [Level of evidence 1b].

Subsequently, another study was published whose objective was to analyse the reduction in the incidence of hip fractures. Named the HIP (Hip Intervention Program) study, it included 9331 women who fulfilled one of the following two criteria: aged 70-79 years, with osteoporosis (n= 5445); or aged > 80 years with at least one clinical risk factor (non-densitometric) for hip fracture. They were assigned to one of 3 the treatment groups indicated in the VERT study, also over 3 years. The results, analysed for all the women, showed that risedronate diminishes the incidence of hip fractures in 30% (IC 95%: 10-40%; p= 0.02). In the group of women with osteoporosis (70-79 years of age) the reduction in risk in those treated with risedronate was 40% (IC95%: 10-60%; p= 0.009). The reduction in risk of hip fracture in the group of women with non-densitometric risk factors (RR: 0.8; IC 95%: 0.6-1.2; p= 0.35), was not, however, significant. The design being identical to the early studies, the supplements of calcium and vitamin D were also of calcium carbonate (1000 mg/day) in a single dose at lunch or dinner, and those who presented low levels of 25 (OH) vit D (< 16 ng/ml or 40 nmol/l) received vitamin D (500 UI/day)[54] [Level of evidence 1b].

Ibandronate has, as its reference study, a study called BONE (Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe). It consist of a randomised double blind study controlled by placebo, and was carried out in 2946 postmenopausal women with a BMD T-score of < -2 in at least one lumbar vertebra (L1-L4), and between 1 and 4 vertebral fractures (T4-L4). Each patient was assigned to one of the following treatment groups: a) 2.5 mg of oral ibandronate daily; b) 20 mg of oral ibandronate on alternate days until 12 doses had been taken, repeated every 3 months; and c) placebo. All the patients received calcium daily, (500 mg of calcium element) and vitamin D supplements (400 UI). By tracking over three years a significant reduction in risk of incidence of new morphometric fractures was noted in the women who took oral ibandronate, both daily (reduction of 62%; p= 0.0001; IC 95%: 43-75) and intermittently (50%; p= 0.0005; IC 95%: 26-65), compared with the placebo group. With respect to clinical vertebral fractures, a reduction in relative risk of 45% was produced in the 2.5 mg ibandronate group and of 48% in the 20 mg group[55] [Level of evidence 1b].

Zoledronate. The last biphosphonate which has been accepted for use in the treatment of osteoporosis is zoledronate, and its reference study is called HORIZON (The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly). It shows a reduction in vertebral and hip fractures in postmenopausal women treated with 5 mg of zoledronate annually, given intravenously, along with daily supplements of calcium (1000 to 1500 mg) and vitamin D (400 to 1200 IU). It was a randomised double blind study in which 3889 women, with an average age of 73 years received 5 mg of intravenous zoldronate, while 3786 women formed the control group. The study lasted 3 years and the principal objectives were the reduction in risk of vertebral and hip fracture. The results showed a decreased risk of vertebral fracture at 3 years of 70% (3.3% in the group treated as opposed to 10.9% in the placebo group), which shows a relative risk of 0.30, with an IC 95% of 0.24 to 0.38, and a reduction in risk of hip fracture of 41% (1.4% in the group treated with zoledronate as opposed to 2.5% in the placebo group; hazard ratio of 0.59, with an IC at 95% of 0.42 to 0.83). The non-vertebral fractures, clinical fractures and clinical vertebral fractures were reduced by 25%, 33% and 77% respectively, with p< 0.001 in all cases[56] [Level of evidence 1b].

Raloxifen. The principal study which demonstrates the efficacy of raloxifen is MORE (Multiple Outcome Research): multi-centric, randomised, double blind, placebo-controlled, carried out in 7705 women with at least 2 years of menopause and who fulfil the densitometric criteria for osteoporosis. The patients were assigned randomly to one of the following treatment groups: a) 60 mg/day of raloxifen; b) 120 mg/day of raloxifen; and c) placebo, and they were followed for 3 years. All the women received, in addition, a supplement of calcium (500 mg/day) and of vitamin D (400-600 UI/day of colecalciferol). At the end of the study the risk of morphmetric vertebral fracture was reduced in both groups treated with raloxifen as against the placebo (raloxifen 60 mg, RR: 0.7; IC 95%: 0.5-0.8; raloxifen 120 mg, RR: 0.6; IC 95%: 0.4-0.7; which supposes a reduction of 30% and 40%, respectively)[57] [Level of evidence 1b].

Calcitonin Calcitonin has its reference study in PROOF (Prospective Reduction of Osteoporotic Fractures) a randomised, double blind, placebo-controlled trial carried out in 1255 postmenopausal women with established osteoporosis. The treatment groups to which they were assigned were: intranasal salmon calcitonin at doses of 100, 200 and 400 UI daily, and a placebo group. All the women received 1000 mg daily of calcium element divided into two doses and 400 UI/day of vitamin D.

This is one of the few studies designed with a follow up of 5 years, at the end of which it was observed that the daily dose of 200 UI salmon calcitonin produced a decrease of 33% in the risk of new vertebral fractures compared with the placebo (RR: 0.67; IC 95%: 0.47-0.97; p< 0.03)[21] [Level of evidence 1b].

Table 4. Pivotal studies with drugs used in the treatment of osteoporosis in postmenopausal women. Principal objective: incidence of fractures

Drug	Name of study	Year	First author (citation)	Group treated	Calcium and Vitamin D	Follow up period
Etidronate	---	1990	Storm (50)	Women with postmenopausal OP	Calcium and vitamin D (quantities NA)	3 years
Alendronate	FIT	1996	Black (51)	Postmenopausal women with BMD with VFx/without VFx	Calcium Carbonate (500 mg/day of calcium element) and vitamin D (250 UI/day) if diet low in calcium (<1,000 mg/day)	3 years
Risedronate	VERT	1999/2000	Harris/Reginster (52/53)	Postmenopausal women < 85 years with at least 2 VFx or one VFx and low DMO (T-score < -2)	Calcium carbonate (1,000 mg/day), and vitamin D (500 UI/day) if 25 (OH) vit D < 16 ng/ml or 40 nmol/l	3 years
	HIP	2001	McClung (54)	Women of 70-79 years and osteoporosis; or aged ≥ 80 years with at least one clinical risk factor for hip Fx		3 years
Ibandronate	BONE	2004	Chesnut (55)	Postmenopausal women with T-score ≤ -2 in at least one lumbar vertebra and between 1-4 VFx	Calcium (500 mg/day) and vitamin D (400 UI/day)	3 years
Zoledronate	HORIZON	2007	Black (56)	Women with densitometric OP with T-score < -2,5 without fractures; or T-score < -2,5 y ≥ 1 VFx	Calcium (100-1,500 mg/day) and vitamin D (400-1,200 UI/day)	3 years
Raloxifen	MORE	1999	Ettinger (57)	Women with ≥ 2 years of menopause with densitometric OP	Calcium (500 mg/day) and colecalciferol (400-600 UI/day)	3 years
Teriparatide	---	2001	Neer (48)	Postmenopausal women with at least one VFx	Calcium (1,000 mg/day) and vitamin D (400-1,200 UI/day)	3 years initially (19 months)
PTH intacta	TOP	2007	Greenspan (49)	Postmenopausal women of 45 to 54 years with T-score < -3; or T-score <- 2,5 plus 1-4 VFx	Calcium citrate (700 mg/day) and vitamin D (400 UI/day)	18 months
Strontium ranelate	TROPOS	2005	Reginster (58)	Postmenopausal women with T-score < -2,5; or, if > 70 years, also with 1 risk of Fx	Calcium (>1,000mg/day) and vitamin D (400-800 UI/ day)	5 years (first 3 years)
	SOTI	2004	Meunier (59)	Postmenopausal women (> 5 years), aged >50 years, with at least 1 VFx and DMO ≤ 0.84 g/cm^2	Calcium (>1,000mg/day) and vitamin D (400-800 UI/day)	3 years
Calcitonin	PROOF	2000	Chesnut (21)	Postmenopausal women with established OP	Calcium (1,000 mg/day) and vitamin D (400 UI/day)	5 years

OP: osteoporosis; BMD: bone mineral density; Fx: fracture; VFx: vertebral fracture; NA: not available

3.4. Calcium and Vitamin D with dual action drugs. Strontium Ranelate

Strontium ranelate is a dual action drug, anabolic and anti-resorptive, with which the TROPOS study was carried out to evaluate its efficacy in the prevention of non-vertebral fractures, and the SOTI study, for the prevention of vertebral fractures.

The TROPOS (Treatment of Peripheral Osteoporosis Study) study was carried out in 5091 postmenopausal women affected by osteoporosis to whom were administered, randomly, either 2 g/day of strontium ranelate or a placebo. All the women received daily supplements of calcium (> 1000 mg) and vitamin D (400-800 UI) before and throughout the study. The study lasted over 5 years, with the first statistical analysis carried out after 3 years. It was observed that the women who received strontium ranelate plus calcium and vitamin D presented a decrease in relative risk for all non-vertebral factures of 16% (p= 0.04) and a decrease of 19% for the most important fragility-related fractures (hip, wrist, pelvis, sacrum, humerus, etc.), with p= 0.031[58]. [Level of evidence 1b].

In the SOTI (Spinal Osteoporosis Therapeutic Intervention) study, 1649 postmenopausal women who had densitometric osteoporosis and at least one vertebral fracture, were included. They were randomised and the group which received treatment was given 2 g of strontium ranelate daily over 3 years. Both the group which had been given the strontium and the placebo group received a supplement of calcium and vitamin D in a similar way as the previous study: depending on the intake of calcium in the diet at least 1000 mg daily of calcium, and, depending on the baseline levels of 25-hydroxivitamin D, a daily dose of 400 to 800 UI of vitamin D, were administered. In the women treated a reduction of 41% in the risk of presenting new vertebral fractures was obtained (RR: 0.59; IC 95%: 0.48-0.73)[59] [Level of evidence 1b].

Table 4 shows a summary of these studies. It is observed that in all of them the drug being studied was always administered with a supplement of calcium and vitamin D.

3.5. Absorption and dosage of calcium and vitamin D

The higher the dose of calcium administered in one go the lower its fractional absorption. Thus, Heaney et al.[60], in healthy volunteers, using radioactive calcium to assess the absorption of calcium, observed that with the administration of 300 mg of calcium 36% of the mineral was absorbed, while if 1000 mg of calcium was administered its absorption was reduced to 23.5%. In the same study, the authors verified that when administered with meals the absorption of salts of calcium (carbonate and citric) was similar.

The same authors carried out a similar study in 24 postmenopausal women to whom they administered an excess of calcium, taken orally, both citrate and carbonate of calcium, in repeated doses, and analysed the increases in total blood calcium, and blood ionic calcium, the decrease in PTH and the increase in the urinary excretion of calcium, arriving at the conclusion that the absorption and bio-availability of the carbonate and citrate of calcium is similar, but that the lower price of the carbonate makes it more recommendable, from a cost-benefit point of view of[61].

On the other hand, different doses of calcium also affect in different ways changes in the levels of PTH. Karkkainen et al. carried out a study in 30 young healthy women to study these dose-dependent effects on the calciotropic hormone and found no evidence of there being more or less benefit in taking them in the morning or the evening[62]. From the physiopathological point of view it would probably be more useful in people with low intake of calcium to divide the daily dose to reduce the levels of PTH and bone resorption[63].

The absorption of calcium is similar, independent of the source. A study carried out by Recker et al. compared the absorption of radioactive calcium (45Ca) in a group of healthy volunteers, administering it through means of whole milk, milk with chocolate, yoghurt, milk substitutes (those prepared using milk derivatives or not), cheese and calcium carbonate. The absorption of calcium varied between 21% and 26% and not one type of administration was significantly superior to the rest[64].

For these reasons the Osteoporosis Society of Canada recommended that calcium supplements be administered in divided doses[65]. More recently, the North American Menopause Society in their 2006 recommendations indicated that to maximise its absorption calcium supplements should be taken in doses of 500 mg of calcium element, or less, throughout the day and with meals[66]. The consumption of calcium supplements with meals can also minimise the possible, although infrequent, secondary effects.

Calcium salts available on the Spanish market

There are various calcium salts which are now available and approved for sale in our country: calcium carbonate, pidolate, phostate, acetate and lactate. There are many pharmaceutical preparations which contain these salts, and their calcium element content varies from one to the other, the most common quantities being between 0.5 and 1g. According to data provided by IMS Health, the company charged with carrying out market studies of pharmaceutical products covering 90% of the country and extrapolated to the rest, calcium carbonate is the type of calcium salt most used in our country, with an annual growth rate higher than the others.

3.6. The importance of complementary therapy in osteoporosis

Adherence to treatment has recently been recognised as a key factor for the successful treatment of osteoporosis[67]. As might be expected, patients who take their medicine for osteoporosis regularly have the best results, both with regard to changes in bone mineral density, and, more importantly, in the reduction in the rate of fractures and decrease in mortality.

Thus, a study published by SIRIS et al.[68] based on a broad population of postmenopausal women over 45 years of age, for whom had been indicated a biphosphonate as treatment for osteoporosis, observed that after 2 years of follow up, those women who took the treatment correctly (43%) had a reduction in risk of fractures, both vertebral and non-vertebral, of 21% compared to the 57% of patients which did not follow the treatment correctly. Similar results had previously been published by Caro et al.[69], who found a reduction in the appearance of new fractures of 16% between those patients who complied as against those who did not. In this study, the follow up period was 2 years, and the drugs being evaluated were calcitonin, THS and the biphosphonates. The same authors repeated this study using a broader database, with a cohort of more than 38000 women affected by osteoporosis, and obtained the same figures: the lack of adherence to treatment was associated with an increase in risk of fracture of 17% after a follow up after 1.7 years[70].

Various studies have also endorsed these results. Hence, McCombs et al.[71] carried out similar work, studying the adherence of a population of 58109 postmenopausal women of more than 55 years of age, diagnosed with osteoporosis, which showed that adherence to treatment over a period of 1 year translates into a greater reduction in risk of fracture, in both hip and vertebrae.

4. Recommendations of the panel of experts

1. There is evidence at the highest level (1st, grade of recommendation A) that calcium and vitamin D supplements themselves reduce the risk of vertebral, non-vertebral and hip fractures, but at a minimum dose of 800 UI/day of vitamin D. In relation to calcium, the maximum benefit is obtained with doses equal to or greater than 1200 mg/day.
2. All the studies carried out with drugs which have been shown to reduce the risk of fracture in menopausal osteoporosis have used calcium and vitamin D supplements, for which reason it is advisable that all drug treatments indicated, be they anabolic, anti-resorptive, or dual action, be administered with calcium and vitamin D supplements. It is recommended that the measures intended to guarantee the compliance with treatment be reinforced and improved.
3. The calcium salts on the market in our country (Spain) for the treatment of osteoporosis are: calcium carbonate, pidolate, phostate, acetate, and lactate, with calcium carbonate being the most used. There are many pharmaceutical preparations which contain these salts, and their calcium element content varies from one to another, with the most common quantities being between 0.5 and 1 g.
4. The absorption of the different calcium salts is similar, as long as they are administered with meals.
5. The ideal model for the administration of calcium is in divided doses and with meals.

Bibliography

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, March 7-29, 2000: highlights of the conference. South Med J 2001;94(6):569-73.
2. Recker RR, Barger-Lux MJ. The elusive concept of bone quality. Curr Osteoporos Rep 2004;2(3):97-100.
3. Becker C. Pathophysiology and clinical manifestations of osteoporosis. Clin Cornerstone 2006;8(1):19-27.
4. Hermoso de Mendoza MT. [Classification of osteoporosis. Risk factors. Clinical manifestations and differential diagnosis]. An Sist Sanit Navar 2003;26 Suppl 3:29-52.
5. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. Lancet 2002;359(9319):1761-7.
6. Tarantino U, Cannata G, Lecce D, Celi M, Cerocchi I, Iundusi R. Incidence of fragility fractures. Aging Clin Exp Res 2007;19(4 Suppl):7-11.
7. Schwab P, Klein RF. Nonpharmacological approaches to improve bone health and reduce osteoporosis. Curr Opin Rheumatol 2008;20(2):213-7.
8. Odvina CV. Osteoporosis: how should it be treated? J Investig Med 2006;54(3):114-22.
9. Zarowitz BJ, Stefanacci R, Hollenack K, O'Shea T. The application of evidence-based principles of care in older persons (issue 1): management of osteoporosis. J Am Med Dir Assoc 2007;8(3 Suppl 2):e51-7.
10. Guyatt GH. Evidence-based management of patients with osteoporosis. J Clin Densitom 1998;1(4):395-402.
11. Boonen S, Body JJ, Boutsen Y, Devogelaer JP, Goemaere S, Kaufman J, et al. Evidence-based guidelines for the treatment of postmenopausal osteoporosis: a consensus document of the Belgian Bone Club. Osteoporos Int 2005;16(3):239-54.
12. Management of osteoporosis in postmenopausal women: 2006 position statement of The North American Menopause Society. Menopause 2006;13(3): 340-67.
13. Maxwell L, Santesso N, Tugwell PS, Wells GA, Judd M, Buchbinder R. Method guidelines for Cochrane Musculoskeletal Group systematic reviews. J Rheumatol 2006;33(11):2304-11.
14. Hosking DJ, Geusens P, Rizzoli R. Osteoporosis therapy: an example of putting evidence-based medicine into clinical practice. QJM 2005;98(6):403-13.
15. Kehoe T. Bone quality: a perspective from the Food and Drug Administration. Curr Osteoporos Rep 2006;4(2):76-9.
16. Gómez de Tejada Romero MJ, Sosa Henríquez M. ¿Qué queremos decir exactamente con "fracturas no vertebrales"? (O ¿por qué no llamar a las cosas por su nombre?). Rev Esp Enf Metabol Oseas 2005;14:39-40.
17. Small RE. Uses and limitations of bone mineral density measurements in the management of osteoporosis. MedGenMed 2005;7(2):3.
18. Meunier PJ. Evidence-based medicine and osteoporosis: a comparison of fracture risk reduction data from osteoporosis randomised clinical trials. Int J Clin Pract 1999;53(2):122-9.
19. Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, et al. Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of postmenopausal osteoporosis. Endocr Rev 2002;23(4):517-23.
20. Adachi JD, Rizzoli R, Boonen S, Li Z, Meredith MP, Chesnut CH, 3rd. Vertebral fracture risk reduction with risedronate in post-menopausal women with osteoporosis: a meta-analysis of individual patient data. Aging Clin Exp Res 2005;17(2):150-6.
21. Chesnut CH, 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000;109(4):267-76.
22. Bouxsein ML. Bone quality: where do we go from here? Osteoporos Int 2003;14 Suppl 5:S118-27.

23. Ragi-Eis S, Zerbini CA, Provenza JR, Griz LH, de Gregorio LH, Russo LA, et al. Is it ethical to use placebos in osteoporosis trials? J Clin Densitom 2006;9(3):274-80.
24. Rosenblatt M. Is it ethical to conduct placebo-controlled clinical trials in the development of new agents for osteoporosis? An industry perspective. J Bone Miner Res 2003;18(6):1142-5.
25. Watts NB. Is it ethical to use placebos in osteoporosis clinical trials? Curr Osteoporos Rep 2004;2(1):31-6.
26. Guyatt G. Evidence-based medicine in everyday practice. Cleve Clin J Med 1999;66(8):461-4.
27. Guyatt GH, Haynes RB, Jaeschke RZ, Cook DJ, Green L, Naylor CD, et al. Users' Guides to the Medical Literature: XXV. Evidence-based medicine: principles for applying the Users' Guides to patient care. Evidence-Based Medicine Working Group. JAMA 2000;284(10):1290-6.
28. Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, et al. Going from evidence to recommendations. BMJ 2008;336(7652):1049-51.
29. Rycroft-Malone J, Seers K, Titchen A, Harvey G, Kitson A, McCormack B. What counts as evidence in evidence-based practice? J Adv Nurs 2004;47(1):81-90.
30. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA 1992;268(17):2420-5.
31. Boonen S, Rizzoli R, Meunier PJ, Stone M, Nuki G, Syversen U, et al. The need for clinical guidance in the use of calcium and vitamin D in the management of osteoporosis: a consensus report. Osteoporos Int 2004;15(7):511-9.
32. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. JAMA 1994;271(1):59-63.
33. Guyatt GH, Sackett DL, Sinclair JC, Hayward R, Cook DJ, Cook RJ. Users' guides to the medical literature. IX. A method for grading health care recommendations. Evidence-Based Medicine Working Group. JAMA 1995;274(22):1800-4.
34. Oxman AD, Sackett DL, Guyatt GH. Users' guides to the medical literature. I. How to get started. The Evidence-Based Medicine Working Group. JAMA 1993;270(17):2093-5.
35. Sackett DL. Evidence-based medicine and treatment choices. Lancet 1997;349(9051):570.
36. Sackett DL. Evidence-based medicine. Semin Perinatol 1997;21(1):3-5.
37. Sackett DL. Evidence-based medicine. Spine 1998;23(10):1085-6.
38. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. BMJ 1996;312(7023):71-2.
39. Barlow DH. Osteoporosis guidelines. Climacteric 2007;10 Suppl 2:79-82.
40. Bartl R. Practical guidelines for the management of osteoporosis: evidence-based and cost-effective. Dtsch Med Wochenschr 2007;132(18):995-9.
41. Compston J. Guidelines for the management of osteoporosis: the present and the future. Osteoporos Int 2005;16(10):1173-6.
42. Geusens PP, Lems WF, Verhaar HJ, Leusink G, Goemaere S, Zmierczack H, et al. Review and evaluation of the Dutch guidelines for osteoporosis. J Eval Clin Pract 2006;12(5):539-48.
43. Johnston CC, Jr. Development of clinical practice guidelines for prevention and treatment of osteoporosis. Calcif Tissue Int 1996;59 Suppl 1:S30-3.
44. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293(18):2257-64.
45. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. Need for additional calcium to reduce the risk of hip fracture with vitamin D supplementation: evidence from a comparative metaanalysis of randomized controlled trials. J Clin Endocrinol Metab 2007;92(4):1415-23.
46. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007;370(9588):657-66.
47. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA 2004;291 (16):1999-2006.
48. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. N Engl J Med 2001;344(19):1434-41.
49. Greenspan SL, Bone HG, Ettinger MP, Hanley DA, Lindsay R, Zanchetta JR, et al. Effect of recombinant human parathyroid hormone (1-84) on vertebral fracture and bone mineral density in postmenopausal women with osteoporosis: a randomized trial. Ann Intern Med 2007;146(5):326-39.
50. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990;322(18):1265-71.
51. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348(9041):1535-41.
52. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282(14):1344-52.
53. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11(1):83-91.
54. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344(5):333-40.
55. Chesnut IC, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19(8):1241-9.
56. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007;356(18):1809-22.
57. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999;282(7):637-45.
58. Reginster JY, Seeman E, De Vernejoul MC, Adami S, Compston J, Phenekos C, et al. Strontium ranelate reduces the risk of nonvertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005;90(5):2816-22.
59. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004;350:459-68.
60. Heaney RP, Dowell MS, Barger-Lux MJ. Absorption of calcium as the carbonate and citrate salts, with some observations on method. Osteoporos Int 1999;9(1):19-23.
61. Heaney RP, Dowell MS, Bierman J, Hale CA, Bendich A. Absorbability and cost effectiveness in calcium supplementation. J Am Coll Nutr 2001;20(3):239-46.

62. Karkkainen MU, Lamberg-Allardt CJ, Ahonen S, Valimaki M. Does it make a difference how and when you take your calcium? The acute effects of calcium on calcium and bone metabolism. Am J Clin Nutr 2001;74(3):335-42.
63. Reginster J-Y, Zegels B, Lejeune E, Michelletti, Kvsaz A, Seidel L, et al. Influence of daily regimen calcium and vitamin D supplementation on pararthyroid hormone secretion. Calcif Tissue Int 2002;70:78-82.
64. Recker RR, Bammi A, Barger-Lux MJ, Heaney RP. Calcium absorbability from milk products, an imitation milk, and calcium carbonate. Am J Clin Nutr 1988;47(1):93-5.
65. Murray TM. Prevention and management of osteoporosis: consensus statements from the Scientific Advisory Board of the Osteoporosis Society of Canada. 4. Calcium nutrition and osteoporosis. CMAJ 1996;155(7):935-9.
66. The role of calcium in peri- and postmenopausal women: 2006 position statement of the North American Menopause Society. Menopause 2006;13(6):862-77.
67. Lekkerkerker F, Kanis JA, Alsayed N, Bouvenot G, Burlet N, Cahall D, et al. Adherence to treatment of osteoporosis: a need for study. Ost 18:1311-7.
68. Siris ES, Harris ST, Rosen eoporos Int 2007 CJ, Barr CE, Arvesen JN, Abbott TA, et al. Adherence to bisphosphonate therapy and fracture rates in osteoporotic women: relationship to vertebral and nonvertebral fractures from 2 US claims databases. Mayo Clin Proc 2006;81:1013-22.
69. Caro JJ, Ishak KJ, Huybrechts KF, Raggio G, Naujoks C. The impact of compliance with osteoporosis therapy on fracture rates in actual practice. Osteoporos Int 2004;15:1003-8.
70. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. Bone 2006;38:922-8.
71. McCombs JS, Thiebaud P, McLaughlin-Miley C, Shi J. Compliance with drug therapies for the treatment and prevention of osteoporosis. Maturitas 2004;48:271-87.

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