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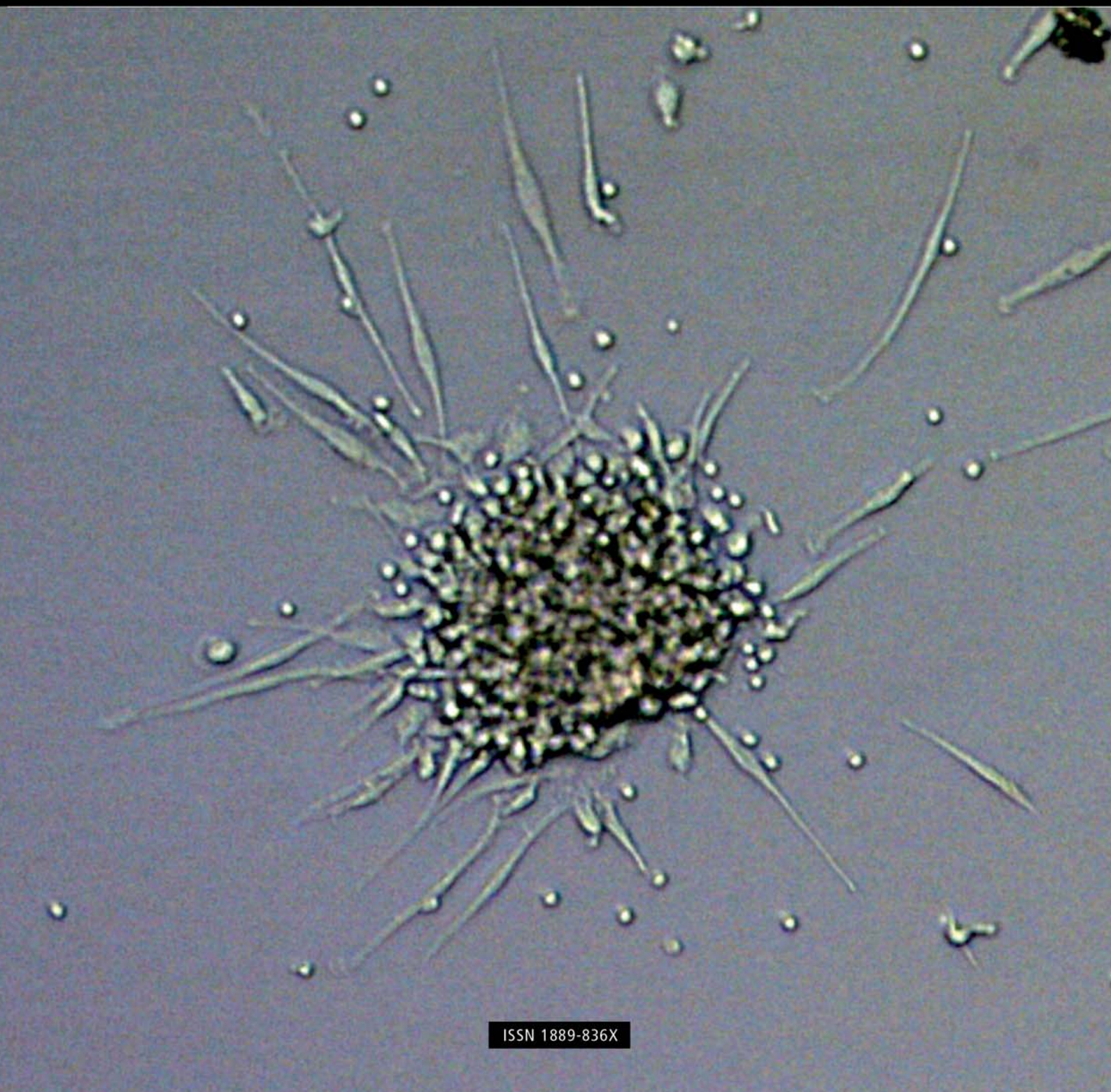

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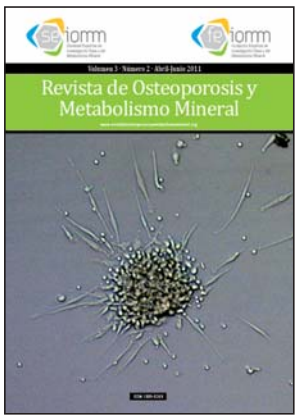

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SUMMARY

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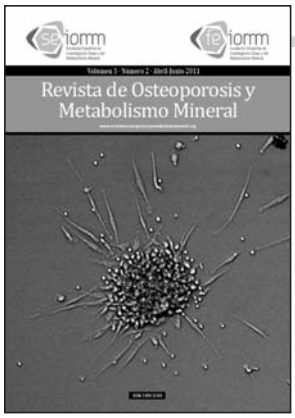

Our cover

Colony expanding mesenchymal stem cells from human bone marrow.

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

Vol. 3 - Nº 2 - April-June 2011

Committee of experts

Osteoporosis in primary care

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Osteoporosis (OP) is a highly prevalent chronic disease which constitutes a public health problem, with significant medical and socioeconomic repercussions due, respectively, to the morbid-mortality which it brings and the direct and indirect costs which it generates. It is expected that with demographic changes which are happening, and the aging of the population, if there is no immediate intervention in clinical practice, the number of patients who will suffer at least one fracture will become greater.

This is a silent disease; there are often neither signs nor early symptoms which alert us to its presence until the fracture occurs. It is these fractures which give clinical importance to the disease: more than half of women and a third of men will experience osteoporotic fractures during the course of their lives.

Free to run its course, the disease follows a chronic and progressive path, in which the appearance of fractures increases notably the risk of new fractures in other places, with the consequent deterioration in the quality of life of the patient. However, we have an opportunity to modify the course of this disease, through preventative measures which help avoid the loss of bone mass and reduce the risk of fracture, and by the treatment of patients with OP with the same aim.

When a pathology reaches the magnitude of osteoporosis, an approach which involves all health professionals is essential. This includes doctors in primary health care, due to their accessibility, the continuity in their dealings with patients throughout their lives, and the general nature of their care.

The majority of patients with osteoporosis should have been attended to in primary care. In order for this to happen, the doctors need to have the knowledge, skills and diagnostic tools which allow the correct management of these patients. There will be certain circumstances in which it will be advisable to refer the patient to a specialist.

It is often difficult to know what is the most appropriate action to take. In part, this difficulty in management lies in the fact that, given the multidisciplinary approach, there is a range of guides to clinical practice and recommendations from different scientific societies. There is little or no doubt in relation to secondary prevention, which is to say that, no patient with an osteoporotic fracture should leave the surgery without an evaluation of the risk of new fractures and an adequate therapeutic plan, with or without the use of drugs. The great difficulty is in finding uniform criteria to be used at the time of treatment in primary care. Until very recently this was solely based on densitometric (DXA) T-score values; the approach currently recommended is to assess the densitometry and clinical risk factors jointly, evaluating the absolute risk of fracture in the following years. All these difficulties in obtaining uniform criteria for assessment, and for indications for treatment, are especially important in primary care, where the difficulty in accessing diagnostic tests (essentially bone densitometry) represents the greatest obstacle. Equally important is the fact that the cost of drugs for antiresorptive treatment has increased notably in our country. In this edition of the review, Martínez and his collaborators analyse how appropriate prescribing is in relation to the recommendations of the guide for the management of osteoporosis in primary care published by SEMFYC in 2002.

Currently, the appearance of the FRAX tool, and the better knowledge of osteoporosis and its various treatments require us to rethink whether to continue in this way, or whether it is necessary to modify the indications as to who to treat, over what period of time, with which drug, etc.

In recent years, different working groups have also carried out studies in this area. All describe populations which are quite similar in primary care clinics in different geographical areas, and similar age groups, around 65 years of age, with a prevalence of previous fracture of 20-25% and with a body mass index (BMI) also similar (above 26-27). However, the variation in terms of whether or not the prescription is appropriate to the recommendations is notable. The work of Martínez et al., observed a percentage of appropriate prescription of biphosphonates of 55%, with 30% in which it was not possible to determine, and 13.7% being inappropriate. They therefore conclude that in less than 15% of cases was the

prescription considered to be inappropriate.

This percentage is much lower than the findings of other works carried out in this country with populations with similar characteristics. Arana Arri[1] found that 26.8% of patients who did not have any risk factor in their history, did however, receive treatment. Of the women who had had a diagnostic test (60% of the total) 42% were inappropriately treated, either excessively or deficiently. And Amaya et al.[2] concluded that the prescription was appropriate to the recommendations in only 25.4% of patients. In the publication by Terol[3], 62% of treatments were not appropriate to the clinical practice guides, without differences between specialisms.

In the work of De Felipe[4], carried out in 212 women treated with antiresorptive drugs, there was a record of densitometry in 73.1% of those treated, and only 51.8% complied with the criteria for treatment.

Finally, Zwart[5] concludes that primary care doctors seldom comply with the guidelines from the guides, and more specifically, the SEMFYC guide for the diagnosis and treatment of osteoporosis. At the same level of appropriateness as Martínez is the work of Pérez[6], which finds a high degree of appropriateness to the SEIOMM guide, both in primary care (71%) and in specialist care (78%), with no significant differences.

We believe the work of Martínez et al. to be highly pertinent, for us, once again, reflecting the necessity of uniform recommendations for our patients, independent of the environment and of the professional by whom they are treated, based on the best possible scientific evidence, both for the diagnosis, as well as for the indication of treatment and most appropriate therapeutic option at that particular time.

Bibliography

1. Arana-Arri E Gutiérrez-Ibarluzea I, Gutiérrez Ibarzaba ML, Ortueta Chamorro P, Giménez Robredo A I, Sánchez Mata AM, et al. Análisis comparativo frente a la evidencia del manejo de la osteoporosis en una comarca de atención primaria. Aten Primaria 2008;40:549-54.
2. Amaya M, Gómez M, Martínez M y Lendínez J. Adecuación del tratamiento preventivo de fracturas osteoporóticas en mujeres posmenopáusicas. SEMERGEN - Medicina de Familia 2008;36:121-7.
3. Terol Moltó C, Quintana-Cerezal J, Santos-Albero MJ, Corell González M, Marcos Martínez P, Crespo Mateos AP. Análisis de la prescripción de antirresortivos en el tratamiento de la osteoporosis en Atención Primaria. Revista Valenciana de Medicina de Familia 2007;24:40.
4. De Felipe R, Cáceres C, Cimas M, Dávila G, Fernández S, Ruíz T. Características clínicas de los pacientes con tratamiento para la osteoporosis en un centro de Atención Primaria: ¿a quién tratamos en nuestras consultas? Aten Primaria 2010;42:559-63.
5. Zwart Salmerón M, Pradera Vilalta M, Solanas Saura P, Gonzalez Pastor C, Adalid Vilar C. Abordaje de la osteoporosis en un centro de Atención Primaria. Aten Primaria 2004;33:183-7.
6. Diez Pérez A, Guañabens Gay N, González Macías J, Jódar E, Muñoz Torres M, Fuster Jensen E. Adecuación del manejo clínico de la osteoporosis a las guías de la SEIOMM. Estudio OPINHO-PC. Rev Esp Enferm Metab Oseas 2008;17:59-65.

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Appropriate use in primary care of antiresorptive drugs against osteoporosis

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Summary
Background: To assess the appropriateness of the prescription of antiresorptive drugs according to the Guide to Osteoporosis of the Spanish Society for Family and Community Medicine (SEMFYC).
Material and methods: Descriptive transversal study carried out in two urban primary care centres. Out of all those patients who had taken an antiresorptive drug and/or had a diagnosis of osteoporosis, a sample of 411 patients was studied. Those who took the drug for other reasons (13), with diagnostic errors (8), *exitus* (3), or lacking clinical history (16) were excluded. Variables were recorded: age, sex, personal and family history of fractures, T and Z densitometric scores, type of antiresorptive drug, calcium and vitamin D supplements, and the specialist who initially indicated treatment. The appropriateness of the prescription was assessed according to whether or not it complied with the criteria in the SEMFYC Guide.
Results: 371 patients complied with the inclusion criteria. Of these, 96.5% were women. The average age was 68 years (standard deviation -SD-: 9.4). In 288 patients (77.6%) the personal antecedence of fractures was assessed, and in 21 (5.7%), that of the family. Densitometry had been carried out in 65.5% of patients. 65.2% had taken biphosphonates, and 14.8%, raloxifene. 72.8% were receiving vitamin D supplements, and 76%, calcium. In 30.5% of cases the treatment was initiated by the family doctor, in 21% by a traumatologist and in 14.3%, by a gynaecologist. In 204 patients (55%) the antiresorptive prescription was appropriate, in 113 cases (30.5%) it was not possible to determine the appropriateness, and in 51 (13.7%) it was inappropriate.
Conclusions: The prescription was inappropriate in fewer than 15% of patients, with biphosphonates the drugs most commonly used. In a third of patients densitometry was not carried out.

Key words: *osteoporosis, Primary care, protocols, biphosphonates, strontium ranelate, raloxifene.*

Introduction

Osteoporosis is a disease of the skeleton characterised by a reduction in bone resistance which exposes the individual to a higher risk of fractures[1]. These fractures are the sole clinical consequence of osteoporosis, appearing in women from their fifth decade of life, and in men, later. In order of clinical importance, these fractures are those of the proximal femur, distal forearm and the spinal column[2,3].

It constitutes a major public health problem given its high prevalence (of 50% in women over 70 years of age)[4] and the socioeconomic repercussions which these fractures have. In Spain, there are 30,000 hip fractures a year[5], their incidence increasing exponentially and becoming a worrying problem in the elderly population. The treatment of these fractures carries a cost of some 720 million euros a year in our country.

We have available an arsenal of antiresorptive drugs (AD), such as the biphosphonates, raloxifene and strontium ranelate amongst others, which have shown a good cost-benefit *ratio*, taking into account the risk of fracture. Various works have shown that we seldom prescribe them in the presence of antecedent fragility fractures[6], and that when we do indicate them, their prescription is not in accordance with the guidance[7]. We have available many recommendations from experts, both national and international, on when we should treat; some consider that the sole criterion is densitometric value, while others (the Spanish Society of Family and Community Medicine, the Spanish Society for bone and Mineral Metabolism Research, the National Osteoporosis Foundation, and many more) consider the diagnostic threshold to be different from the treatment threshold, and, as well as bone mass, consider the presence of other risk factors.

These drugs carry a high health cost. As an example, in Catalonia in the year 2008 the pharmacy costs of drugs for use against osteoporosis represented 35% of the cost of specialised drugs (some 485 million euros out of a total of 1,388 million euros).

For all these reasons, we would like to see to what extent the prescription of these drugs is appropriate to that set out in the Guide to Osteoporosis of the Spanish Society of Family and Community Medicine (SEMFYC) published in 2008[8].

Material and methods

A transverse descriptive study was carried out in two health centres in the urban area of the city of Barcelona which serves a population of 45,851 inhabitants, of whom 22.7% are older than 65 years of age. Women of 50 years or more represent 44.9% of the total of women, and men of 60 years or more, 26.2% of all the men.

Using the computerised clinical history records system of the centre at the start of 2007, all those patients who had had a diagnosis of osteoporosis recorded (categories CIE 10 M80 and M81, M82 and their subcategories) were identified. Using the computerised prescription system, all the patients who had taken any AD (alendronate, risedronate, raloxifene, strontium ranelate or calcitonin) were listed, obtaining a total of 1,806 patients with a recorded diagnosis of osteoporosis and/or currently using an AD. For the calculation of the sample size, in the absence of previous studies, a test pilot study was carried out, which observed an adequacy rate of 65%. Accepting an alpha risk of 0.5 in a bilateral contrast as a proportion, the sample size was calculated of 411 subjects, assuming that the population is the total, and a reposition rate of 0.25. Reasons for exclusion were considered to be diagnostic errors, absence of clinical history, those who took ADs for other reasons and those who were deceased. A simple random sampling was carried out.

The paper and computerised clinical histories were reviewed and the following data were gathered: age, sex, personal (PAF) and familial (FAF) antecedence of fracture, maximum values of T and Z scores (in the lumbar spine L2-L4, femoral neck and total hip) in the first bone densitometry carried out through dual X-ray absorptiometry, the specialisation of the doctors who initiated the treatment and who carried out the follow up, the type of AD, supplements of calcium and vitamin D and the appropriateness of the prescription. This last variable was defined as *appropriate* when it complied with the criteria of the Guide to Osteoporosis of SEMFYC (Figure 1) and an AD needed to be taken, *inappropriate* when they did not comply, and *indeterminate* when not all the data needed to evaluate it were available. The *inappropriateness* criterion included two subcategories: *a lack* (when an AD needed to be taken but was not prescribed) and *an excess* (when an AD was given but should not have been taken).

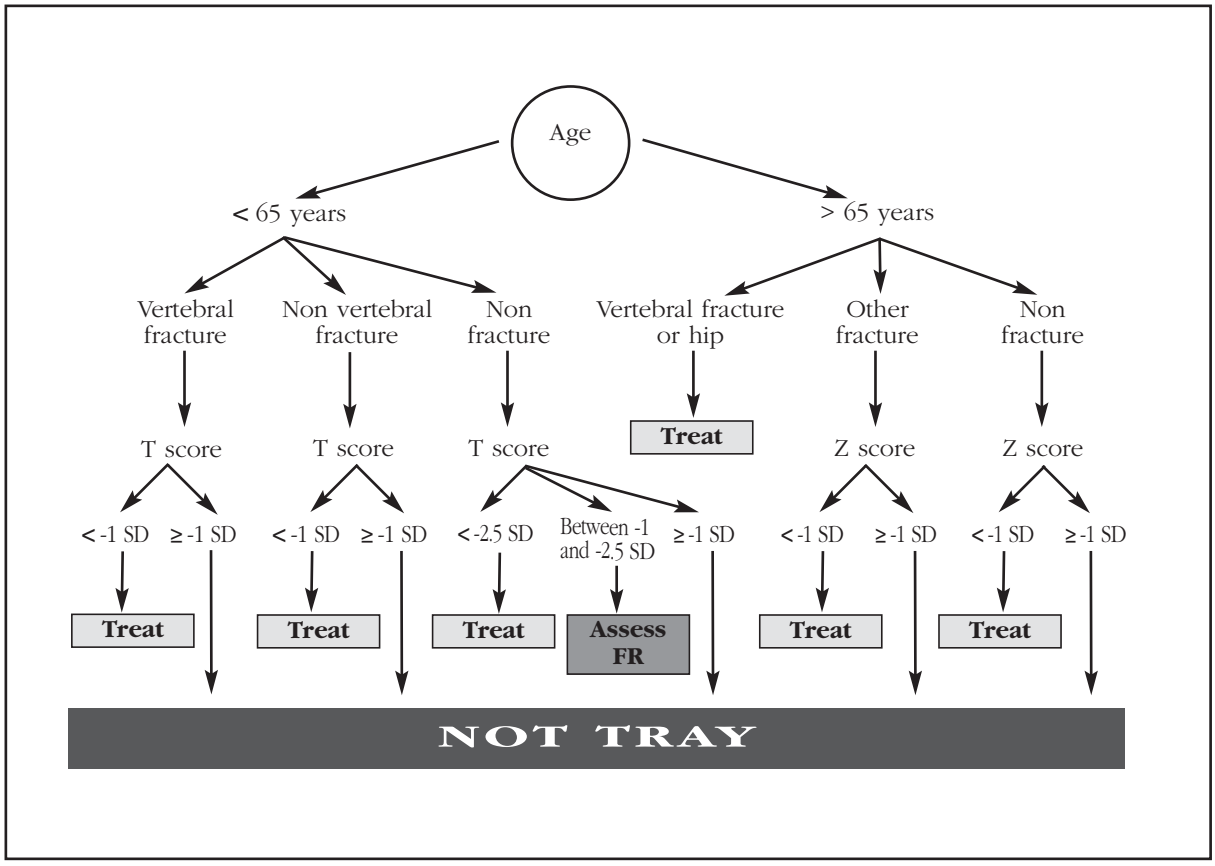
The SPSS.11 software package was used for the analysis. The results were presented with measures of central tendencies and with absolute and relative frequencies for the qualitative variables. To study the differences between the groups the chi squared (χ^2) test was used with $p < 0.05$.

Results

Of the 411 patients studied, 40 (9.7%) were excluded (8 due to diagnostic error, 16 for absence of history, 13 for taking ADs for other reasons and 3 due to *exitus*), leaving 371 patients.

The average age of the a patients was 68 years (SD: 9.4); 96.5% were women. 247 patients (66.6%) had a diagnosis of osteoporosis recorded in its different CIE-10 categories: osteoporosis with pathological fracture (M80) in 53 patients (21.4%), osteoporosis without pathological fracture (M81) in 193 patients (78.1%), and osteoporosis in diseases classified in other places (M82) in one case (0.5%). Densitometry was performed in 243 subjects (65.5%), 167 cases of which complied with the diagnostic criteria for osteoporosis according to the definition of the WHO (Table 1). In 288 patients (77.6%) personal history of fracture had been recorded (Table 2), and in 20 (5.4%) a familial antecedent. The specialist who most frequently initiated the treatment and carried out the follow

Figure 1. Algorithm for therapeutic decisions in osteoporosis (adapted from the SEMFYC Guide 2000)



up was the family doctor (GP), followed by the rheumatologist (R), the traumatologist (T) and the gynaecologist (G) (Figure 2).

With respect to treatment, 242 patients (65.2%) took biphosphonates 55 (14.8%) raloxifene, 11 (3%) strontium ranelate, 5 (1.3%) calcitonin and 1 patient (0.3%) was prescribed more than one associated AD. 57 patients (14.4%) took no AD. In terms of calcium and vitamin D supplements, 282 (76%) and 270 (72.8%) patients, respectively, received them.

In analysing by subgroups of prescribing doctor (Figure 3), biphosphonates and raloxifene continued to be the most commonly used ADs, with statistically significant differences being observed between the gynaecologists and the other specialists (χ^2= 20.29; p<0.05) in favour of a higher use of raloxifene on the part of the gynaecologist.

In 204 patients (55%) the prescription was defined as appropriate, and in 51 (13.7) as inappropriate (31 by lack of AD and 20 due to its excess). By specialist, (Figure 4), no statistically significant differences were observed between appropriateness and inappropriateness (χ^2= 4.19; p>0.05). 116 cases (31.3%) were indeterminate. In analysing the principal causes of indeterminacy it was observed that 83 patients did not have densitometry in their clinical history, and 45 had personal history of fracture.

Discussion

There are various consensus guides about when antiresorptive drugs should be used in osteoporosis in our ambit. The choice of the criteria proposed by the SEMFYC is due to the fact that it does not only consider the T- and Z-score densitometric values as the sole criterion for the recommendation of treatment, but it also values other risk factors, which are, principally, age and personal history of fracture. So not only is bone mineral density taken into account but other risk factors for osteoporosis, which allows the selection of a high risk population, thus increasing the positive predictive value of densitometry.

In analysing the appropriateness of the prescription we observe that in little more than 13% of cases was the prescription inappropriate, and if we considered only those patients who had been prescribed some antiresorptive drug (314 cases) we find that 6.4% should not have taken them. In our ambit there are few works which have assessed the appropriateness of prescription; Zwart et al.[7] showed that in women between 50 and 80 years of age it is only considered to be justified in 8%, data disparate from those observed by us, where the appropriateness was 55%.

We find a high number of cases where the prescription was indeterminate. If we consider

Table 1. T-score and Z-score values observed by age subgroups in patients who had densitometries

		≤ 70 years (n=143)	> 70 years (n=100)	Total (n=243)
T score				
	< -2.5	94 (65.7%)	73 (73%)	167 (68.7%)
	Between –1 and –2.5	25 (17.5%)	8 (8%)	33 (13.6%)
	> -1	2 (1.4%)	1 (1%)	3 (1.2%)
	Not stated	22 (15.4%)	18 (18%)	40 (16.5%)
Z score				
	< -1	25 (17.5%)	9 (9%)	34 (14%)
	≥ -1	8 (5.6%)	16 (16%)	24 (9.9%)
	Not stated	110 (76.9%)	75 (75%)	185 (76.1%)

Table 2. Personal history of fractures noted in clinical history

		Absolute frequency	Relative frequency
Fracture		**89**	**24%**
	Vertebral	46	51.7%
	Hip	3	3.4%
	Multiple	12	13.5%
	Other	28	31.4%
Non fracture		**199**	**53.6%**
Not stated		**83**	**22.4%**

only those cases in which we have been able to determine the appropriateness (in 255 patients) we observe that in 20 patients (7.8%) who took an AD it would not be indicated. One of the principal limitations which we faced in designing this study was the known under-recording of computerised clinical histories. This was taken into account at the time of design of the study in the patient selection and data-gathering phases. In the selection, all those patients who had taken an AD were also reviewed so as not to miss patients who had not been recorded correctly (in a third of those cases studied there was no diagnosis of osteoporosis). In the data gathering phase it was decided to review also paper-based clinical histories so as not to lose any information.

There were no significant differences in terms of appropriateness of prescription between specialists, and those that were seen were in terms of the use of ADs between gynaecologists and the other specialists, the former using raloxifene to a greater extent. In a study carried out in Navarra[9]

Figure 2. Medical specialisation of the professionals who initiated the treatment (prescriber) and who carried out the follow up

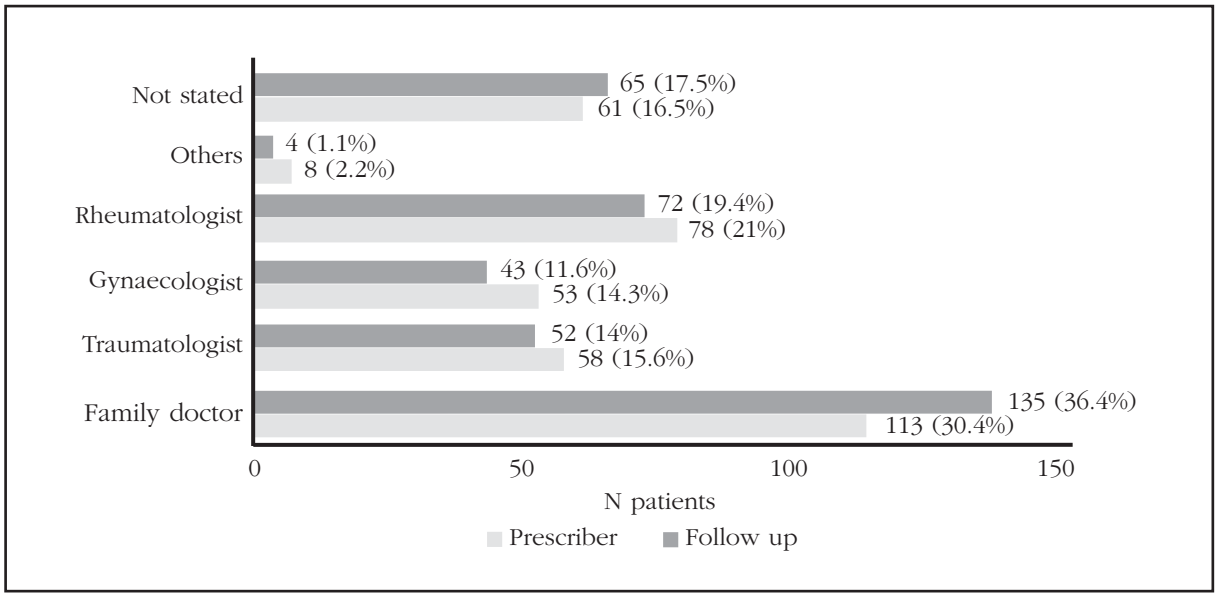
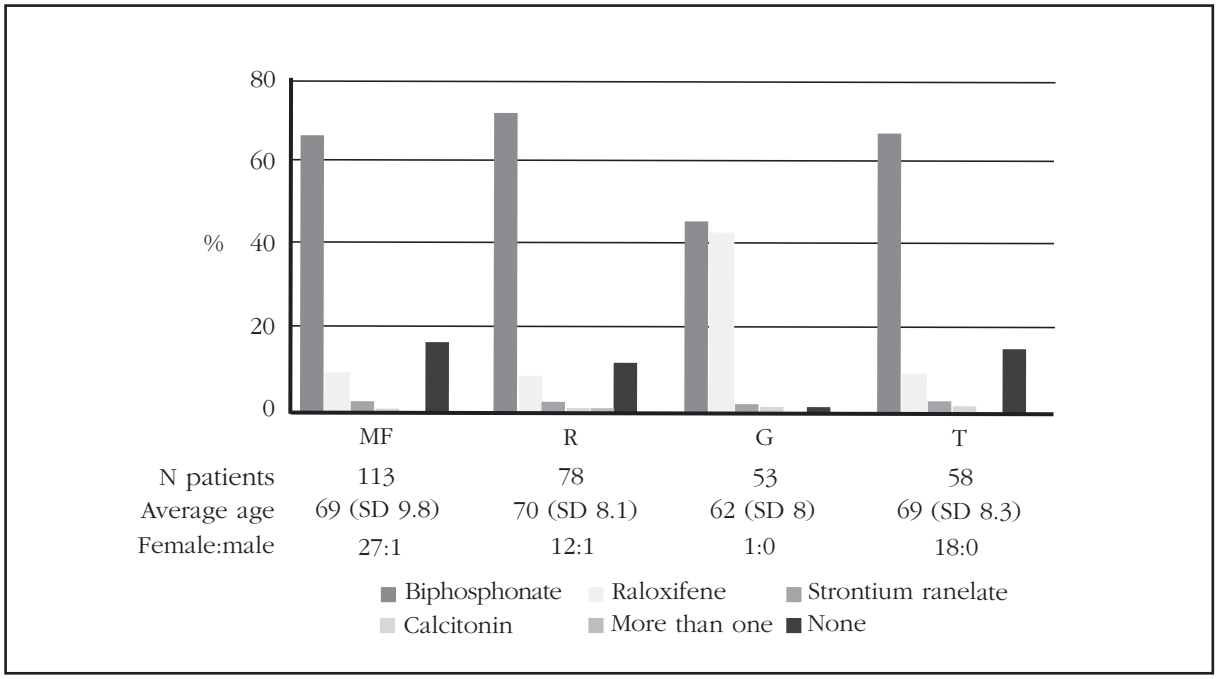


Figure 3. Types of antiresorptive drugs according to professional prescriber

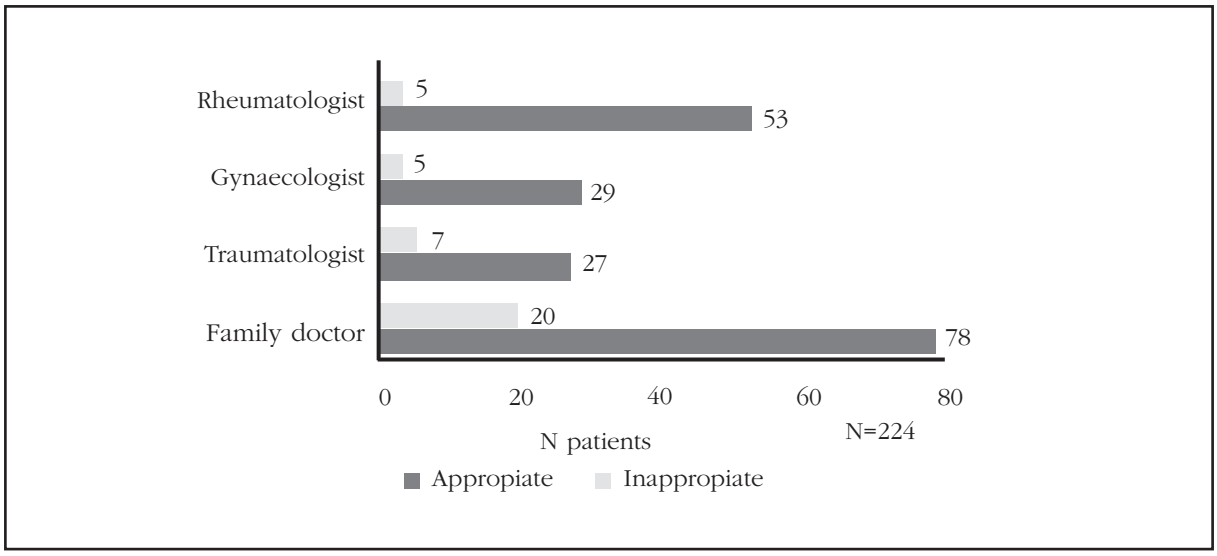


on the use of drugs for osteoporosis, a greater use of raloxifene was also observed on the part of gynaecologists. It may be possible to explain this by its role in the reduction in the incidence of oestrogen receptive positive invasive breast cancer in low risk women[10], and for treatment of a younger population (average age 62 ± 8 years) where vertebral fracture is more significant than that of the hip[11]. Raloxifene has been shown to reduce the risk of suffering vertebral[12], but not non-vertebral, fractures.

With respect to the use of calcium and vitamin D, three out of every four patients received supplements. This addresses two modifiable risk factors for osteoporosis[13,14], of which there is evidence that substitutive treatment in patients with a low intake of calcium and low levels of vitamin D would have an preventative effect on fractures, in particular in the population of elderly and institutionalised women[15,16].

In spite of the high level of accessibility of densitometry (100% in our centres) a low level of

Figure 4. Degree of appropriateness of the prescription according to medical specialism



actual performance of this procedure was found (in 6 out of every 10 cases), even though some societies such as the National Institute for Health and Clinical Excellence (NICE)[17] are certainly recommending the use of biphosphonates in secondary prevention to treatment of women of 75 years of age with previous fractures without the need to carry out densitometry. In our study this would mean 14 women out of a total of 128 not having densitometry. Recently PAPPS, in their recommendations[18], propose an algorithm for taking decisions in the prevention of fractures in women, in which they also recommend initiating treatment before the presence of certain risk factors (personal history of peripheral fractures at over 50 years of age, history of morphometric vertebral fractures, family history of hip fracture and body mass index below 19 kg/m^2), without the need for densitometry in women over 60 years of age. Since the carrying out of our work a new version of the SEMFYC Guide has been published[19], which introduces as new elements in the therapeutic algorithm the consideration of treatment before the presence of earlier fractures, and, in their absence, consideration of the T values and other risk factors (maternal history of fracture, high risk of falls and low weight).

Finally, we mention that in this work appropriateness does not make reference to the fact that one or other AD may be more or less effective in the prevention of fractures, or may have a higher or lower level of cost-effectiveness, since there are already many studies[12,20-22] which endorse these effects, which are not covered in the objectives of our work.

Thus we may conclude that, in spite of the problems we have found in the clinical history data records , in those cases in which we were able to determine the appropriateness of the prescription, this was high. The publication of new recommendations raise, for us, the possibility of appropriateness at the present moment. We think that perhaps in the design of a future study it would be more interesting to contact patients to gather data on the different risk factors, thus minimising the loss of information. On reflection, it would also be interesting for each professional to think about the possible causes of the poor recording of data.

Bibliography

1. NHI Consensus. Delevopement Panel on Osteoporosis Prevention, Diagnosis and Therapy. JAMA 2001;285:785-95.
2. Documento de la Sociedad Española de Reumatología. Rev Esp Reumatol 2001;28:148-53.
3. Espallargues M, Estrada MD, Samprieto-Colom L, Granados A. Cribado de la osteoporosis en las personas mayores. Med Clin (Barc) 2001;116:77-82.
4. Díaz Curiel M, García JJ, Carrasco JL, Honorato J, Pérez Cano R, Rapado A, et al. Prevalencia de osteoporosis determinada por densitometría en la población femenina española. Med Clin (Barc) 2001;116:86-8.
5. Rapado A, Díaz M. Manual Práctico de osteoporosis en Atención Primaria. Madrid: FHOEMO,1996.
6. Alarcón Alarcón T, González Montalvo J. Osteoporosis en el anciano: una preocupante falta de tratamiento. Med Clin (Barc.) 2002;118:515.
7. Zwart M, Fradera M, Solanas P, González C, Adalid C. Abordaje de la osteoporosis en un centro de atención primaria. Aten Primaria 2004;33:183-7.
8. Grupo de Osteoporosis de la SEMFYC. Osteoporosis. Guía de abordaje. Recomendaciones SEMFYC. Barcelona: EdiDe, 2000.
9. Evirti J. Utilización de fármacos para la osteoporosis. An Sist Sanit Navar 2003;26:107-21.
10. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Mershon J, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA 1999;281:2189-97.
11. Cabasés Hita JM, Carmona López G, Fernández Vecino R. Incidencia, riesgo y evolución de las fracturas osteoporóticas de cuello de fémur en las mujeres en España, a partir de un modelo de Markov. Med Clin (Barc) 2000;114:63-7.

12. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK. 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;282:637-45.
13. Mezquita P, Muñoz M, López F, Martínez N, Conde A, Ortego N, et al. Elevada prevalencia de déficit de vitamina D en poblaciones con riesgo de osteoporosis: un factor relevante en la integridad ósea. Med Clin (Barc) 2000;119:85-9.
14. Cheung AM, Feig DS, Kapral M, Díaz-Granados N, Dodin S, and the Canadian Task Force on Preventive Health Care. Prevention of osteoporosis and osteoporotic fractures in postmenopausal women: recommendation statement from the Canadian Task Force on Preventive Health Care. CMAJ 2004;170:1665-7.
15. Valecillo G, Díez A, Carbonell J, González J. Tratamiento de la osteoporosis con calcio y vitamina D. Revisión sistemática. Med Clin (Barc) 2000;115:46-51.
16. Avenell A, Gillespie WJ, Gillespie LD, O'Connell DL. Vitamina D y análogos para la prevención de fracturas asociadas con la osteoporosis senil y postmenopáusica (Revisión Cochrane traducida). En: La Biblioteca Cochrane Plus, 2007 Número 2. Oxford: Update Software Ltd.
17. Bisphosphonates (alendronate, etidronate, risedronate), selective oestrogen receptor modulators (raloxifene) and parathyroid hormone (teriparatide) for the secondary prevention of osteoporotic fragility fractures in postmenopausal women. The National Institute for Clinical Excellence. London: 2005.
18. Arribas L, Alonso P, Ballón E, Coutado A, del Cura I, Fuentes M, et al. Actividades preventivas en la mujer. Aten Primaria 2007;39:123-50.
19. Sanfélix Genovés J, Giner Ruiz V. Osteoporosis: Manejo en Atención Primaria. Barcelona: Ediciones SEMFYC, 2008.
20. Cranney A, Wells G, Willan A, Griffith L, Zytaruk N, Robinson V, et al. Meta-analysis of Alendronate for the Treatment of Postmenopausal Osteoporosis. The Osteoporosis Methodology Group and the Osteoporosis research Advisory Group. Endoc Rev 2002;23:508-16.
21. Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, et al. Meta-analysis of Risedronate for the Treatment of Postmenopausal Osteoporosis. The Osteoporosis Methodology Group and the Osteoporosis research Advisory Group. Endoc Rev 2002;23:517-23.
22. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski J, Spector T, et al. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal fracture. N Eng J Med 2004;350:459-68.

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Evaluation of the absolute risk of fracture by means of tool FRAX® in a Spanish cohort

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Summary

The FRAX® tool has been developed as an aid to predict the 10-year probability of hip and major osteoporotic fracture using country-specific data. This algorithm combines clinical risk factors with or without the bone mineral density (BMD) measurement to identify subjects in high risk of fragility fracture. The aim of this study was to challenge the Spanish version of the WHO fracture risk assessment tool FRAX® on a cohort of women with BMD measurement indication.

*Methods:*Clinical and BMD data from a large population cohort taken from metropolitan area of Barcelona were used for this study. Inclusion criteria were: age range 40-90 yrs, clinical risk factors, femoral neck BMD T-score available and follow-up longer than 7 years. Main outcome was: major osteoporotic fracture at least 7 years after the first BMD measurement. The total number of predicted fractures by the FRAX algorithm was compared with the total number of new registered fractures during the follow-up time in the study population and expressed as observed - expected fracture (O/E) ratio. Results were stratified by age; BMD results and number of clinical risk factors were included in the FRAX algorithm.

Results: 8450 women were included, 69% were under 60 years and 14% presented a previous fracture. After follow-up, 10% had a major osteoporotic fracture. Wrist was the most incident fracture site and hip accounted only for 0.9% of the total. The 52% of the main fractures happened in women with none or only one risk factor. The fracture ratio (O/E) was 0.8 [CI 95%: 0.7 ; 1.1] for hip fractures and 3.1 [CI 95%: 2.8 ; 3.5] for the main osteoporotic fractures. The O/E ratio was lower as higher was the age of women (for those older than 70 O/E=1.9 [CI 95%: 1.6 ; 4.3]), longer the follow-up time (for those with more than 10 years O/E=2.7 [CI 95%: 2.2 ; 3.4]) or fewer number of risk factors (O/E=3.2 [CI 95%: 2.7 ; 3.9]).

Conclusions: The Spanish version of the FRAX® algorithm for this population is reasonably well adjusted to predict hip fractures but underestimates the observed main osteoporotic fracture incidence, independently of the T-score, and number of risk factors.

Key words: o*steoporosis, fractures, absolute risk, FRAX, double energy X-ray absorptiometry, DXA, Spanish population.*

Introduction

The preoccupation in the clinical management of osteoporosis with criteria for cost-effectiveness has shown up the necessity to improve the identification of the people who will benefit from specific treatment. This concern has stimulated the development of procedures for evaluating the risk of fracture using the principal risk factors.

The estimation of the risk of fracture is the most rational approach for taking therapeutic decisions regarding a patient with suspected bone fragility.

The group of experts in bone metabolism diseases who collaborate with the World Health Organisation (WHO) have developed an instrument for identifying those persons at highest risk of fracture in the period of 10 years subsequent to the evaluation. The new instrument, called FRAX®, combines the principal factors for risk of fracture with the alternative of incorporating measurement of bone mineral density (BMD) when this is available[1].

The FRAX® tool has been developed by a group of researchers led by Prof. John Kanis, with the support of many experts and scientific organisations. To facilitate its application the authors have carefully selected those risk factors which should be included, limiting them to those which have the greatest ability to predict fractures. The tool is accessible through an internet portal: (http://www.shef.ac.uk/FRAX).

Among those factors related to fractures, reduced BMD has been identified as one of the main ones due to its close relationship with bone resistance. Other factors have been identified which also contribute significantly to the risk of fracture. Notable amongst those are: family antecedence of fragility fractures, personal history of fragility fractures, low body weight, the habit of smoking and age. This last factor reinforces the negative effect of reduced BMD, or of other factors, it being one of the most significant predictors of fracture independent of BMD.

The degrees of risk which FRAX® uses for the prediction of osteoporotic fractures have been derived from the combination of multiple studies of the incidence of fractures in different cohorts. The studies of the incidence of femoral fractures are the most frequent, due to the fact that, in the majority of cases, these events require hospitalisation or surgical intervention, elements which are easily traceable in health records. With the object of compensating for the lower level of availability of data on other fractures, the FRAX® model assumes that the *ratio* between femoral fractures and other osteoporotic fractures is similar in different populations, accepting this *ratio* as a constant. This constant was obtained from studies carried out in the population of Mälmo (Sweden)[2,3].

This element which currently characterises FRAX® is presumed to allow the application of the model to different countries in which different incidences of hip fracture are recognised[4]. At present, version (3.1) of FRAX® allows the calculation of the absolute risk of fracture for the populations of 26 countries in 5 continents.

FRAX® estimates the risk of fracture for one of the four principal osteoporotic fractures, which are fracture of the proximal femur, of the wrist, of the proximal third of the humerus and vertebral fractures. The region of the femur receives special attention, with individualised evaluation, due to its clinical importance, and because of the greater quality of the epidemiological data.

With the aim of adapting the FRAX® model to the Spanish population, the authors have used information published on the incidence of proximal femoral fractures recorded in Barcelona (1984), the Canaries (1990), Zamora (1991), in prospective studies in Seville and Madrid (1989), and on the incidence in Cantabria with follow up over a long period of time[4]. A representation of a number of studies on the incidence of hip fractures in various regions of Spain is shown in figure 1, indicating those which were used in the development of FRAX®.

The importance of the application of the version of FRAX® for Spain in our community requires the validation of the tool.

The aim of this study is the assessment of the version of the FRAX® tool developed for Spain for the calculation of the individual's absolute risk of fracture over a period of 10 years in a cohort of the female population with indications for the carrying out of a bone densitometry (BD).

Material and method

The ability of the FRAX® tool designed for Spain to predict fractures was evaluated in a cohort of the female population followed in successive visits over a period of time longer than 7 years. The design corresponds to a retrospective longitudinal study. The cohort was made up of women older than 40 years of age with indications for bone densitometry and from whom had been gathered, during their follow up visits, information on the incidence of bone fractures.

During their first visit a BD of the hip and spine was carried out following a specific protocol, as well as a structured interview and a validated survey of calcium consumption. The results of the femoral bone measurements from the first visit and the clinical risk factors (CRF) considered by FRAX® were estimated.

Measurement of bone mineral density

The acquisition method was adjusted to the measurement protocol recommended by the makers of the measurement equipment, using the measurement of the region of interest in absolute values (g/cm^2) and as a T-score (comparison of the result of the measurement with respect to reference values obtained from the healthy Spanish population between 20 and 40 years of age). During the period of time covered by this study different measurement equipment was used from the same manufacturer Lunar Corp. - GE Healthcare Madison WI, US (models: DPX, DPX-L and Prodigy).

Population of the study

For the selection of the participants in the cohort the CETIR (Centre for Technical Studies with Radioactive Isotopes) database was used. This is a medical centre in the city of Barcelona dedicated to diagnostic imaging and in which bone densitometries using the technique of dual energy X-ray absorptiometry (DXA) have been carried out since 1989. The database systematically brings together the principal clinical risk factors and the BMD in the femoral neck since 1992.

At each visit questions from an epidemiological questionnaire were asked, taking anthropometric measurements. The questionnaire gathered data about family and personal history of osteoporosis, co-morbidity, treatments, period of application, bone fractures, smoking habits, consumption of alcohol and of calcium, calculating this last element using a questionnaire about eating habits. The indication for the measurement of BMD was made in accordance with the presence of CRFs, following the strategic lines of selective screening proposed by the clinical guides published in Spain and reports of the Catalan Agency for the Evaluation of Technology and Medical Research[5-7].

The inclusion criteria were: 1) female sex, 2) a measurement of bone mineral density having been taken in the proximal third of the femur, 3) availability of valid data from an epidemiological survey from the first visit, and 4) availability of follow up with more than one visit after the first baseline study, during a period of time which coincides with the period of up to 10 years foreseen by the FRAX® tool, after the first visit.

Table 1. Clinical risk factors. Percentages of the total cohort analysed

Clinical risk factors		n	%
Age (years)	< 60	5,831	69.0
	60-69	2,267	26.8
	≥ 70	352	4.2
Body mass index (kg/m^2)	< 25	3,317	39.3
	25-30	3,741	44.3
	> 30	1,392	16.5
Family antecedents of fractures		2,101	24.9
Personal antecedents of osteoporotic fractures		1,146	13.6
Corticoids		254	3.0
Rheumatoid arthritis		74	0.9
Current smoking habit		596	7.1
Alcohol consumption		3	--
T-score in femoral neck	>-1	2,745	32.5
	-2.5 a -1	4,490	53.1
	<-2.5	1,215	14.4
Number of risk factors:	0	124	1.5
	1	4,733	56.0
	2	2,901	34.3
	3	583	6.9
	≥ 4	109	1.4

Using these criteria a cohort of women was selected in whom had been carried out measurements of BMD in the upper third of the femur between January 1992 and February 2009, using the aforementioned DXA (dual energy X-ray absorptiometry) densitometers.

All the BD examinations were carried out within a set protocol in which were recorded the biographical data of the patient, information about the method used in the DXA measurement, indication of the test, medical report, questionnaire on the presence of principal clinical risk factors, toxic habits, lifestyle, gynaecological history, treatments and intake of calcium calculated by means of a questionnaire about the dietary use of the main foods which contain calcium, and its frequency. The main variable of the study was the presence of fragility fractures observed during the follow up. At each visit the patient was asked about the number and location of fractures which had occurred since the last visit. The osteoporotic fractures which FRAX® assesses are found in the upper third of the femur, in the vertebrae, in the wrist and in the humerus. Other fractures attributed to bone fragility, such as those of the pelvis, ribs, fingers, etc., were not considered in this study[3]. The vertebral fractures recorded were always those which

Table 2. Estimation of the hazard *ratios* of total fracture of the principal risk factors

Variable	HR	CI 95%
Age (≥ 60, < 70 years)	2.0	1.7 ; 2.3
Age (≥ 70 years)	2.5	1.9 , 3.3
Family antecedence of osteoporosis or fracture	1.1	1.0 ; 1.3
Secondary osteoporosis	2.3	1.7 ; 3.1
Rheumatoid arthritis	2.7	1.7 ; 4.3
Antecedents of osteoporotic fractures[1]	1.5	1.2 ; 1.9
Corticoids	2.0	1.5 ; 2.7
Nuliparity (no gestation of more than 6 months)	0.94	0.8 ; 1.2
No maternal lactation	1.1	0.9 ; 1.2
BMI: overweight or sedentary obesity (≥ 25 kg/m^2)	1.2	1.1 ; 1.4
Sedentariness	1.2	1.0 ; 1.4
Tobacco consumption: active smoker	0.8	0.6 ; 1.1
Low daily intake of calcium (<500 mg/day)	0.8	0.6 ; 1.0

1: personal antecedence of fracture of the humerus, forearm, vertebra and/or hip.
HR: hazard *ratio*; IC 95%: confidence interval of 95%

could be confirmed by radiography or by analysis of vertebral fracture using DXA. The diagnosis of vertebral deformity fractures was carried out using Genant's semi-quantitative method, which is used to diagnose vertebral deformity when there is a loss of one of the three vertebral heights of the vertebral body (using the lateral projection) of at least 20%. The method classifies the fractures according to type of deformity and their severity (a reduction of 20-25% in anterior, medial or posterior height, Grade I or light; loss of 25-40%, Grade II or moderate; and if the loss is higher than 40%, Grade III or severe)[8].

Fractures associated with moderate or severe trauma were excluded. The result of the BMD was recorded as a T-score and stratified in three categories: normal BMD (T-score >-1); low bone mass (T-score between -1 and -2.5); and osteoporosis (T-score <-2.5).

The personal history recorded any pathologies which the patient had suffered and the drugs they were consuming or had consumed, as well as the personal and family history of osteoporotic fractures and of osteoporosis. With the aim of adapting to the FRAX® model, those pathological antecedents which contribute secondarily to the reduction of bone mass (hyperparathyroidism, diabetes *mellitus*, anorexia nervosa, anaemia, hyperthyroidism, gastrectomy, etc.) were selected. Antecedence of rheumatoid arthritis, or the intake of glucorticoids were recorded in a differentiated way. Data on gynaecologicial history were registered, such as age of menarche and age of menopause, number of gestations (of over 6 months), maternal lactation and antecedence of hysterectomy continued to be recorded. Finally, the following variables were taken into account: level of physical activity (sedentariness, yes/no). Consumption of tobacco (active smoker, ex-smoker or non-smoker) and daily intake of calcium (expressed in mg/day).

The probability of proximal femoral fracture and of the main regions of the skeleton were calculated for each woman using the FRAX® tool in its version for Spain.

Statistical analysis

An initial descriptive analysis was carried out, calculating the frequencies and percentages for each of the categorical variables. For the quantitative variables the average and standard deviation (SD) was calculated. To determine the association between the different risk factors and the study's main variable (osteoporotic fracture), the relative risk (RR) was calculated with the confidence interval (CI) corresponding to 95%, using the Cox model. To evaluate the predictive capacity of the FRAX® model the *ratio* of the fractures expected from the model, as a result of the sum of the probabilities of fracture for each patient, to the number of fractures observed in the follow up period was calculated. Similarly, the ROC (Receiver Operating Characteristics) curves were estimated to evaluate the capacity to predict fractures using solely the CRFs or the measurement of BMD, and the FRAX® tool which combines the CRFs and the measurement of the BMD in the femoral neck.

The results are considered to be statistically significant with p value of $p<0.05$. The statistical software package Stat 11.0 for Windows was used for the management of the data and in the statistical analysis.

Results

The CETIR database includes 190,939 records of first BD carried out in different women from January 1992 to February 2008. Applying inclusion and exclusion criteria, a sample was obtained of 171,408 (90%) women, of whom 50,106 (29%) had at least one follow BD.

A follow up of 5-6 years was reached in 14.9% of cases, of 7-8 years in 9.3%, 9-10 years in 4.8% and over 10 years follow up in 2.8% of cases. With the aim of having a sufficient number of cases the decision was taken to position the minimum threshold for follow up at 7 years after the first visit, with 17% (8,450 women) complying with this requirement. The average period of follow up in the cohort selected was 9.2 years (7-14.5 years).

The average age was 55.9 years (±7.4 SD). 69.1% of the cohort were younger than 60 years of age and only 4.2% were more than 70 years of age. The average age of onset of menarche was 13 years (±1.6 SD) and the average age at which menopause had started was 46.4 years (±5.9 SD).

A description of the principal risk factors for osteoporosis are shown in table 1. It is notable that 24.9% had family antecedence of osteoporosis or of osteoporotic fracture, and 3% had taken corticoids. 13.6% of the women included in the study were found to have had at least one antecedent osteoporotic fracture. The most frequent fractures prevalent were those of the forearm (627 fractures), the antecedent which, out of the whole sample, is present in 7.4% of the cases. In relation to obstetric history, 12.9% had had no gestation of over 6 months and 40.2% had not had maternal lactation on any occasion.

The description of the modifiable risk factors shows that 39.2% of the women studied had a BMI lower than 25 kg/m^2, and 70.6% had a level of physical activity which was sedentary, or of low intensity. 7.1% declared themselves to be active smokers, and 7.7 said they had a daily intake of calcium lower than 500 mg/day.

With respect to the measurement of BMD in the femoral neck, 14.4% of the cohort was classified

Table 3. *Ratio* of total observes fractures to those predicted with the FRAX® model

Total	OBS	PRE	O/P	CI 95%
	842	353	2.4	2.1 ; 2.7
BMD				
Normal	184	57	3.2	2.4 ; 4.4
Osteopenia	449	178	2.5	2.1 ; 3
Osteoporosis	209	117	1.8	1.4 ; 2.2
Age				
< 55	275	101	2.7	2.2 ; 3.5
55-65	354	143	2.5	2 ; 3
65-75	201	100	2.0	1.6 ; 2.6
≥ 75	12	8	1.4	0.5 ; 4.3
Risk factors				
< 2	443	138	3.2	2.7 ; 3.9
2-3	373	203	1.8	1.6 ; 2.2
≥ 4	25	12	2.0	1.1 ; 4.9

OBS: observed. PRE: predicted. O/P: observed/predicted *ratio*. CI 95%: confidence interval of 95%. Risk factors: BMI<20, personal antecedence of fracture, family antecedence of fracture, smoker, rheumatoid arthritis, corticoids, secondary osteoporosis and alcohol

Table 4. *Ratio* of hip fractures observed to those expected with the FRAX® model

Hip	OBS	PRE	O/P	CI 95%
	72	88	0.8	0.6 ; 1.1
BMD				
Normal	7	2	2.7	0.6 ; 12.1
Osteopenia	34	34	1.0	0.6 ; 1.6
Osteoporosis	31	51	0.6	0.4 ; 0.9
Age				
< 55	8	14	0.6	0.2 ; 1.4
55-65	31	31	1.0	0.6 ; 1.6
65-75	31	37	0.8	0.5 ; 1.3
≥ 75	2	5	0.4	-0.2 ; 3.2
Risk factors				
< 2	38	32	1.2	0.7 ; 1.9
2-3	29	51	0.6	0.3 ; 0.9
≥ 4	5	4	1.2	0.1 ; 25.6

OBS: observed. PRE: predicted. O/P: observed/predicted *ratio*. CI 95%: confidence interval of 95%. Risk factors: BMI<20, personal antecedence of fracture, family antecedence of fracture, smoker, rheumatoid arthritis, corticoids, secondary osteoporosis and alcohol

as osteoporotic, and 53.1% showed reduced bone mineral density (T-score between -1 and -2.5).

In the information collected during the follow up regarding specific antifractural treatments (with calcitonin, hormone replacement therapy, oestrogen receptor modulators, tibolone, etidronate, alendronate, risedronate and strontium), distinct from calcium and vitamin D, can be seen in 13.0% of women aged less than 55 years received one of the therapies indicated; in the group between 55 and 65 years of age 18.5% received some type of treatment; those between 65 and 75 years of age, 19.6%; and in women over 75 years of age 35.7% were treated. Overall, 16.2% of the cohort received antifractural treatment with at least one of these therapeutic agents during the follow up period. In terms of calcium and vitamin D supplements, what is notable is the progressive increase in the number of patients treated according to age. Among women aged below 55 years 12.9% received supplements; of those between 55 and 65 years, 24.1%; of those between 65 and 75 years, 35.8% and in women older than 75 years, 50.0%.

Figure 2 shows the results of the BMD, stratifying the cohort by baseline age of the patients. The BMD (and the T-score) diminished inversely with an increase in the age of the population. At the start of the decade of the 50s, 5.4% of the cohort was classified as osteoporotic (T-score equal to or lower than -2.5), reaching 46.0% in those women over 70 years of age.

In the follow up, 10.0% of the patients suffered an osteoporotic fracture in one of the principal regions of the skeleton (proximal femur, vertebrae, humerus, forearm). The forearm was the region which suffered a high incidence of fractures (4.5%), while the upper third of the femur only represented only 0.9% of the total. 9.1% of the women who did not have less than two risk factors suffered an osteoporotic fracture. On the other hand, 22.9% of the women who had four or more risk factors evaluated with FRAX® suffered from one of the principal osteoporotic fractures. The rate of incidence of fractures in the cohort of the Spanish population is 11 fractures/1,000 patients/years.

Table 2 presents the relative risk for the different factors studied in relation to the risk of fragility fracture. An age of over 70 years is the factor which has a hazard *ratio* (HR) of greatest magnitude (2.5 [CI 95%: 1.9 ; 3.3]), followed by antecedence of rheumatoid arthritis, secondary osteoporosis, consumption of corticoids and personal history of osteoporotic fracture.

Tables 3 and 4 show the principal fractures, and those of the hip, observed during the follow up and those expected according to the FRAX® model. The *ratio* of the hip fractures observed to those predicted by FRAX® is similar (O/E = 0.8 [CI 95%: 0.6;1.1]). For the main osteoporotic fractures, the number of fractures observed is a little more than double that foreseen by the FRAX® model (O/E = 2.4 [CI 95%: 2.1; 2.7]). This underestimation is reduced among women of greater age or with a greater risk of fracture.

Figures 3 and 4 show the ROC curves and the area under the curve when the predictive capacity of the FRAX® models and of the BD is estimated. In this cohort the two measurements have an area under the ROC curve similar to that for the hip fracture, 0.77 and 0.74 respectively. Whereas, for the total fractures the result is slightly lower (FRAX® model = 0.62 and BD = 0.61).

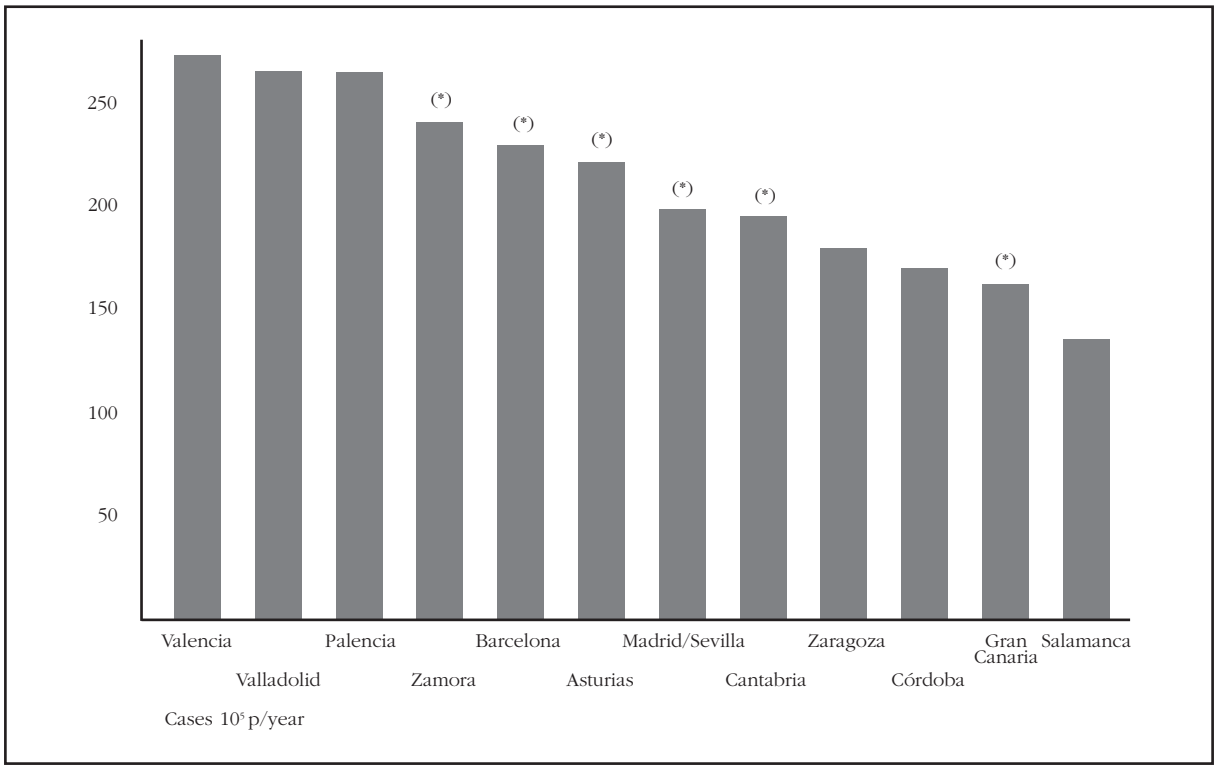
Discussion

The development of the FRAX® tool is, without a doubt, a significant advance in the clinical management of osteoporosis. From a practical point of view it is certainly an achievement to be able to estimate the risk independently of the measurement of bone density, but a calculation would be better. In the current version, the bone measurement is limited to a single region of interest, the femoral neck. This element may, potentially, limit the capacity of the tool to identify subjects with high risk. Another controversial characteristic is the assessment of the CRFs; some of these are assessed globally, such as history of previous fractures (no matter if they be single or multiple) or the accumulated dose of corticoids. Its application remains limited to women who have not received earlier treatment. Despite these limitations, it represents an instrument designed to help the taking of therapeutic decisions which has enormous potential in the approach to osteoporosis in Spain[9]. As with any new method or instrument, its application in our community needs to pass through a process of validation and adjustment.

The validation of the FRAX® model means checking that the number of fractures predicted coincides with the number of fractures actually occurring over the period of 10 years. In addition, the process of evaluation of the fractures which occur requires prolonged and complex follow up with large sample sizes. Since its recent promulgation there have been studies in other countries aimed at the validation of FRAX®. On this basis an appropriate way of using the FRAX® tool in the Canadian population has been proven. In turn, in a group of the French population, the female cohort of the OFELY study, it can be seen that the incidental fractures observed over a period of 10 years showed a relationship with the age of the patients, and with low BMD similar to that foreseen by the FRAX® tool. However, in women aged over 64 years with low bone density (T-score <-1), FRAX® undervalued the number of fractures predicted by 48% in relation to those observed in this cohort, which requires a revision of the algorithm to adjust it to the French population[10-12].

In this retrospective follow up study in a broad group of the Spanish population the *ratio* of the rate of fractures observed to those predicted by the FRAX® tool (O/E) for the region of the femur is 0.8% [CI 95%: 0.6; 1.1], a value close to the "ideal" scenario in which the number of fractures predicted by the FRAX® toll is similar to the number of fractures observed in the Spanish population. Various plausible explanations may be offered

Figure 1. Studies of incidence of femoral fracture in different regions of Spain



which would justify this performance in hip fractures, such as maybe the significantly higher average age of the femoral fractures, the limiting of mobility after this type of fracture, as well as the known fact of the increase in mortality, which together would impede the prolonged follow up of these patients. However, the small proportion of cases of fractures of the femur in the cohort studied necessitates caution with the projection of the result.

Advanced age and reduced BMD (lower T-score) are factors associated with a higher rate of osteoporotic fractures, including those of the femur. BMD stands out as one of the principal risk factors, with a greater predictive capacity of new fractures than the other CRFs, although with FRAX® it is seen as an optional factor, since there is still limited access to bone densitometry for wide sections of the population.

In the evaluation of its diagnostic performance by estimating the sensitivity and specificity (ROC curves) of the FRAX® model in which are combined the CRFs and BMD, a slightly better performance can be seen when CRFs and BMD are combined, compared with the use of BMD alone, although the difference is small (area below the curve of 0.77 vs 0.74 for hip fractures, and 0.62 vs 0.61 in the principal osteoporotic fractures) in relation to that originally developed based on a Swedish population[2].

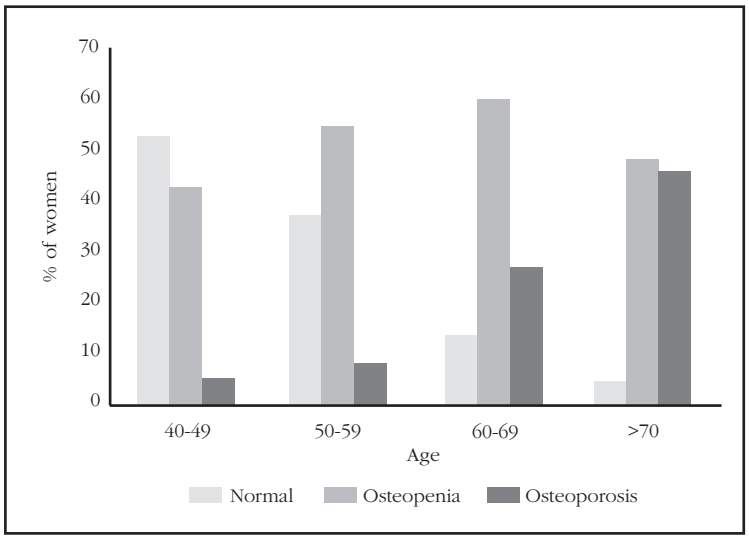
In vertebral fractures, those cases which have been confirmed by radiography have been used. From 1998, the response protocol in medical centres considered the carrying out of an analysis of vertebral fractures by means of a DXA study (thoracic and lumbar spine lateral projection) in those cases where there was a reduction in height of greater than 2 cm compared to an earlier visit, of 4 cm compared to historic height remembered by the patient, or suspicious evidence in the PA projection of the lumbar spine. All in all, it is assumed that a proportion of vertebral fractures are not recorded in the follow up period.

The number of fractures recorded in the follow up period probably could have been higher if the patients had not received treatment, or if all the vertebral fractures had been recorded. In spite of the fact that the cohort was selected on the basis of indications for bone densitometry, the number of patients who received some kind of antifractural therapeutic agent was relatively modest (20.7%), and similar to the percentage of patients in which this was accompanied by calcium of vitamin D supplements (23.2%).

The rate of principal osteoporotic fractures observed was higher than the level of fractures predicted by FRAX® (observed, 842 vs predicted, 353), O/P *ratio* = 2.4 [CI 95%: 2.1 : 2.7]. The undervaluation of fracture in the main regions of the skeleton was independent of the T-score reached, or of the number of CRF's present.

The O/P fracture *ratio* maintained an inversely proportional relationship to the age of the women, such that at greater ages the difference between observed and predicted fractures tends to dimi-

Figure 2. Percentages of women with osteoporosis as a function of their age



nish. It is also observed that there is a slight reduction in the difference when the follow up period is longer (in the follow up periods longer than 10 years the O/P = 2.7 [CI 95%: 2.2 ; 3.4]) or when a high number of risk factors coincide (for those cases without any risk factors O/P = 4.2 [CI 95%: 3.5 ; 5.3]).

The FRAX® model evaluated predicts the principal fragility fractures in only a third of patients evaluated. There are, at the moment, no other studies which evaluate the performance of FRAX® in our population applying a similar method. Despite this, it is interesting to highlight the fact that this tendency has also been observed in the ECOSAP study[13,14]. In this study a follow up was made over 3 years of a cohort composed of 5,201 women. The application of FRAX® showed some similar results, despite the fact that the methodology used was different. The quantitative ultrasound method was used for the bone measurements and the follow up period was less. The authors confirmed a good performance for FRAX® for femoral fractures with a O/P fracture *ratio* ≈ 1, but maintaining an underestimation of risk of principal osteoporotic fractures with a O/P *ratio* ≈ 2.

The fact that there is a coincidence in the incidence of femoral fractures, and a high coincidence with the average rate of hip fractures which come from the epidemiological studies selected for FRA® in Spain can be deduced from The performance of FRAX® in the two cohorts of Spanish women. Similarly, both studies indicate that the FRAX® tool does not properly estimate the global risk of fracture (principal osteoporotic fractures).

In the absence of consistent epidemiological studies on the incidence of other fragility fractures, both studies suggest that the relationship between femoral fractures and the principal osteoporotic fractures in our population is different to that applied by the FRAX® model originating in Sweden[2,3].

The number of women who have been subject to such a prolonged follow up only consist of 17% of those women in whom a first BD was carried out. This small share of patients is due in great measure to the selection of the patients. Those women who display the most risk factors or who have a more precarious state of health receive greater medical attention, and therefore a closer follow up.

On the other hand, the suspicion that not all fractures occurring in the cohort were recorded (especially vertebral fractures) and the potential protective capacity of the specific treatments which were followed for some time of the follow up period by 19.5% of the cohort, gives support to the idea that the O/P fracture *ratio* could be even more unbalanced.

One aspect not considered in the results of this study is the performance of FRAX® in the Spanish male population. The validation of the FRAX® model in the female population, which deals with CRF and BDM measurements, means that the prediction of fractures in a prolonged period of time coincides reasonably well with the rate of fractures observed. At present, the model developed for Spain has performed as an imperfect tool which needs to be adapted for its application in our population.

Conclusion

The WHO's method for arriving at the rate of osteoporotic fractures in Spain is, in general, consistent with the observational clinical data for femoral fractures. However, the current version of the FRAX® tool underestimates the incidence of the other osteoporotic fractures, independently of the T-score, the number of risk factors and the follow up time. What is required, therefore, is a greater number of epidemiological studies of the incidence of the principal osteoporotic fractures to explain these differences.

Bibliography

1. Kanis JA, on behalf of the World Health Organization Scientific Group. Assessment of Osteoporosis at the Primary Health-Care Level. Technical Report. WHO Collaborating Centre for Metabolic Bone Diseases. University of Sheffield, Sheffield, UK. World Health Organization. Summary Report of a WHO Scientific Group. WHO, Geneva. www.who.int/chp/topics/rheumatic/en/index.html
2. Kanis JA, Johnell O, Oden A, Sembo I, Redlong-Johnell I. Dawson A, et al. Long-term risk of osteoporotic fracture in Malmö. Osteoporos Int 2000;11:660-74.
3. Kanis JA, Johnell O, Oden A, Dawson A, De Laet C, Jonsson B. Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds. Osteoporos Int 2001;12:989-95.
4. Kanis JA, Johnell O, De Laet C, Jonsson B, Oden A, Oglesby A. International variations in hip fracture probabilities; Implications for risk assessment. J Bone Miner Res 2002;17:1237-44.

Figure 3. Area under the ROC curve from the FRAX® model (curve configured by means of points joined by lines) and the result of the BD (bone density, in the point curve graph) for hip fracture

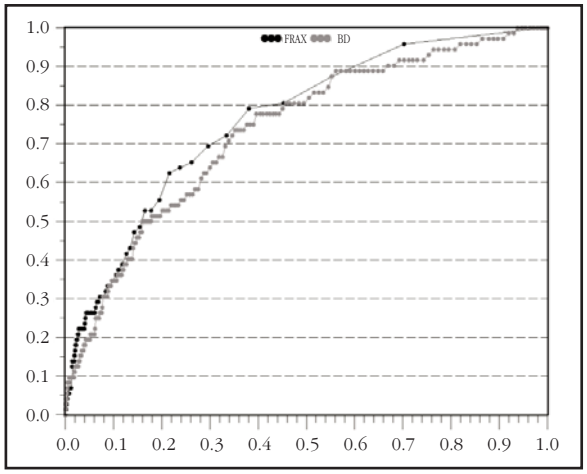
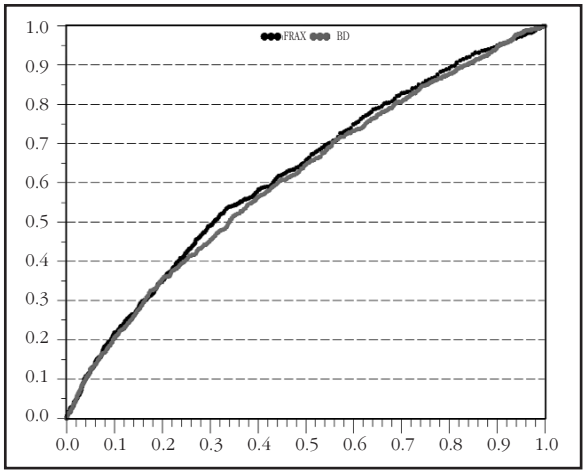


Figure 4. Area under the ROC curve from the FRAX® model (coloured black) and the result of the BD (bone density, coloured grey) for the total of fractures



5. González-Macías J, Guañabens N, Gómez C, en representación del Comité de expertos de SEIOMM para elaboración guías. Guías de práctica clínica en la osteoporosis postmenopáusica, glucocorticoidea y del varón. Sociedad Española de Investigaciones Óseas y Metabolismo Mineral. Rev Clin Esp 2008;208(Supl 1):1-24.
6. Espallargués M, Sampietro-Colom L, Estrada MD, Solà M, del Río L, Setoain J, et al. Identifying bone-mass-related risk factors for fracture to guide bone densitometry measurements: A systematic review of the literature. Osteoporos Int 2001;12:811-22.
7. Estrada MD, Ferrer A, Borrás A, Benítez D, Espallargués M. Guía para la indicación de la densitometría ósea en la valoración del riesgo de fractura y el control evolutivo de la osteoporosis. Actualización Diciembre 2004. Barcelona: Agència d'Avaluació de Tecnología i Recerca Mèdiques. CatSalud. Generalitat de Catalunya. Febrero 2006 (GPC01/2006).
8. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res 1993;8:1137-48.
9. Díez Pérez A. El debate sobre la escala FRAX. Rev Osteoporos Metab Miner 2010;2:1.
10. Leslie WD, Lix LM, Johansson H, Oden A, McCloskey E, Kanis JA, et al. Independent clinical validation of a Canadian FRAX® tool: Fracture prediction and model calibration.J Bone Miner Res 2010;25:2350-8.
11. Sornay-Rendu E, Munoz F, Delmas P, Chapurlat R. The FRAX tool in French women: how well does it describe the real incidence of fracture in the OFELY cohort. J Bone Miner Res 2010;25:2101-7.
12. Trémollieres FA, Pouillès JM, Drewniak N, Laparra J, Ribot CA, Dargent-Molina P. Fracture risk prediction using BMD and clinical risk factors in early postmenopausal women: sensitivity of the WHO FRAX tool. Bone Miner Res 2010;25:1002-9.
13. Vila J, Marín F, González-Macías J, Martín D, Tojeiro S, Díez-Pérez A, en representación de los investigadores del proyecto ECOSAP. Validation of an algorithm to calculate the absolute risk of non-vertebral fragility fractures in a cohort of postmenopausal women. Med Clin (Barc.) 2009;133:501-5.
14. González-Macías J, Villa J, Marín F, Díez-Pérez A. Análisis del comportamiento predictivo de la herramienta FRAX en la cohorte de 5.201 mujeres del Estudio ECOSAP. Rev Mult Gerontol 2009;19:11.

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Structural study using micro-CT of the femur of Goto-Kakizaki rats, experimental model for non-overweight type 2 diabetes

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Summary

B*ackground:* The effects of type 2 diabetes on the microstructure and mass of bone are not clearly defined. The objective of this study has been to assess the microstructural properties and volumetric bone mineral density of Goto-Kazizaki rats, the rat model for non-overweight type 2 diabetes which tries to circumvent the influence of obesity on bone mass.

Material and methods: An experimental study was designed using Goto-Kazizaki rats compared with a control group of non-diabetic Wistar rats of similar weight and with normal glycemia, with densitometric and microstructural studies being carried out on the distal region of the femur using computerised X-ray microtomography (micro-CT).

Results: In the volumetric densitometry no significant differences were found between the two groups. The microstructural study showed that the BV/TV and trabecular connectivity were reduced in the diabetic rats, while the tube-like trabeculae increased to the detriment of plaque-like trabeculae.

Conclusion: The deterioration trabecular bone quality could explain the decrease in biomechanical bone resistance in type 2 diabetes.

Key words: *type 2 diabetes, X-ray microtomography, bone mineral density, bone microstructure.*

Introduction

Skeletal disorders in diabetes are different according to whether one is dealing with type 1 or type 2 diabetes. Those patients with type 1 diabetes have a decrease in bone mass which implies an increased risk of fracture[1,2], whilst type 2 diabetes may present bone mass which is increased, reduced or within normal limits[3,4]. However, the risk of fracture in type 2 diabetes is increased[5,6]. This fact could be due to causes both inside, and outside, the bone (retinopathy, neuropathy, drugs, etc) which determine a higher incidence of falls. One fact common in type 2 diabetics is overweight, which constitutes a confusion factor due to the fact that weight is a determining factor of bone mass. Obese people normally have raised bone mineral density. To avoid the influence of this confusion factor an experimental study was designed with Goto-Kakizaki (GK) rats, a substrain of non-obese Wistar rats which develop type 2 diabetes. GK rats have a light to moderate type 2 diabetes which occurs after birth, and develop chronic complications of the disease such as neuropathy and nephropathy[7].

The main objective of this study was the assessment using computerised micro-tomography of the densitometry and the trabecular and cortical microstructural properties of GK rats, and to compare them with a group of Wistar rats used as a control, with the intention of evaluating, and in their case, defining, the changes which in these variables induce obesity.

Material and methods

Animal model

An experimental study was carried out with 4 male GK rats as against a control group of 4 male non-diabetic Wistar rats of a similar weight and with normal glycemia (Taconic Farms Inc. Lille Skensved, Denmark), due to the fact that the Goto-Kakizaki substrain was developed from the Wistar rats. The treatment of the animals and all the experiments were carried out in accordance with Law 14/2007 and with Royal Decree 1201/2005, and following the guidelines of the UNE-EN 30993-3:1994 rules and ISO 10993-2:2006. The rats were fed with a standard diet and had free access to water, did not received any drug treatment, and were sacrificed at 12 weeks in a chamber with CO_2.

Microstructural analysis of the bone using micro-CT

Once the animals were sacrificed, the right femurs were extracted in order to carry out the structural analysis. After the extraction, the samples were wrapped in gauze soaked in saline solution and conserved at -20°C until the last moment before analysis. The microstructural analysis of the samples was carried out using computerised X-ray microtomography (micro-CT), using the commercial equipment SkyScan 1172 (SkyScan NV, Aarstelaar, Belgium) in the Trabeculae® research laboratory, Empresa de Vase Technologia, S.L (Ourense, Spain).

The distal region of each femur was scanned with an X-ray source of 50 KV and an intensity of 200 µA, using a voxel size of 8.95 µm. An aluminium filter of 0.5 mm in thickness was positioned to reduce beam hardening artefacts. The rotation step used was 0.4° up to a total of 180° and the exposure time was 1250 ms.

The images obtained were reconstructed using the modified Feldkamp algorithm[8], using the NRecon 1.5 software application (SkyScan NV, Aarstelaar, Belgium). The transverse sections resulting from the reconstruction stage were used for the quantitative analysis of the trabecular and cortical bone microstructure, using the application CTAn 1.10.0.1 (SkyScan NV, Aarstelaar, Belgium), after their segmentation into binary images using locally adapted thresholding[9].

For the analysis of the trabecular bone a metaphyseal-diaphyseal region of interest (cortical bone excluded) of 2.5 mm was selected, starting at a distance of 1.0 mm from the growth plate in a proximal direction. For the analysis of the microstructural properties of the cortical bone a region of interest of 1.0 mm was taken, starting at 4.0 mm from the growth plate (Figure 1).

The quantitative variables which were determined for the trabecular region were: volumetric bone fraction (BV/TV), specific bone surface (BS/BV), bone surface density (BS/TV), trabecular thickness (Tb.Th), trabecular separation (Tb. Sp), trabecular number (Tb.N), trabecular pattern factor (Tb.Pf), structural model index (SMI), and degree of anisotropy (DA). The different variables were measured directly using methods described in the literature[10,11]. The non-metric variables, SMI and Tb.Pf, were calculated directly from the three dimensional model. The SMI indicates the relative prevalence of plate-like or rod-like trabeculae, with a higher presence of plates being indicated the nearer its value is to zero[12]. For its part, Tb.Pf is an inverse index of connectivity, measured from the calculation of the relative convexity or concavity of the bone surface[13]. A higher value of Tb.Pf the trabecular network shows a poorer connectivity, which also implies a reduction in mechanical resistance. The DA is a measure of the alignment of the trabeculae in a determined direction, calculated in such a way that 0 is complete isotropy and 1 is complete anisotropy.

In the case of the cortical region, the parameters calculated included: cortical thickness (Ct.Th), the average transverse area of the bone (B.Ar), the average polar inertial moment (I) and the eccentricity (Ecc). I is a basic index of mechanical resistance which indicates the resistance to rotation of a transverse section in a determined axis (assuming uniform biomechanical properties). Ecc is a parameter which indicates the difference in elongation of a transverse section with respect to a circular form (a circle is considered to be an ellipse with zero eccentricity).

Determination of volumetric bone mineral density

Using the images obtained though micro-CT, the volumetric bone mineral density (BMDv) was

determined, both in the cortical and trabecular regions. Direct calibration was used with attenuation coefficients of calcium hydroxyapatite models of known density (250 and 750 mg/cm^3). The method of calculating the BMDv differed slightly in different areas of the bone, since in the case of the trabecular region it refers to a volume of bone and medullar tissue, whilst in the case of the cortical region it was limited to a volume occupied solely by calcified lamellar bone.

Statistical analysis

The data obtained were put into a text database which was exported to the statistical software package IBM SPSS Statistics 19 (IBM Corporation, Somers, NY, US) for their subsequent statistical analysis. The individual results were reviewed in order to avoid loss of data and unusual values. Then the descriptive analysis of the variables of the study was proceeded with. The descriptive statistics of the numerical variables were expressed as an average ± standard deviation, maximum value and minimum value.

The comparative statistical study of the numerical data was carried out by means of an single factor variance analysis (ANOVA) and the Tukey HSD test for multiple comparatives. In those cases which did not comply with homogeneity of variance criteria, the Broen-Forsythe test was applied for the variance analysis and the Games-Howell test for the multiple comparatives.

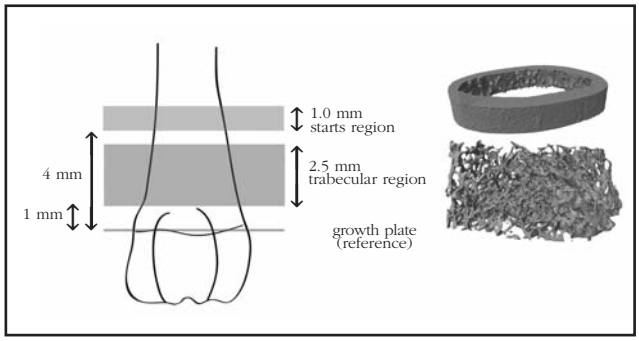
The level of statistical significance was established at values of $p<0.05$ for all the variables analysed.

Results

The GK rats had a weight of 385 ± 23 g and glycemia of 195 ± 84 mg/dl, which confirms the presence of diabetes in this group, while the Wistar rats had a weight of 395 ± 35 g and glycemia of 124 ± 15 mg/dL ($p<0.01$). The results of the bone mineral density volumetry are reflected in Table 1. BMDv did not show differences between the two groups, neither in the cortical section, nor the trabecular. Although there appears to be a loss of trabecular bone mass in the diabetic rats, this did not reach significant levels, probably due to the sample size used, or the development time of the diabetes.

Table 2 shows the results of the microstructural variables in the trabecular region. Statistically significant differences were observed in the volumetric bone fraction (BV/TV), indicating a loss of trabecular bone in the diabetic rats as compared with the control group. The considerable increase in Tb.Pf in the GK rats confirms, also, a significant loss of trabecular connectivity in diabetes. On the other hand, the increase in SMI shows a prevalence of tubular trabeculae in diabetic rats in comparison with the control group, in which plate-like trabeculae predominate. Although the BS/TV, the Tb.Th and the Tb.N are reduced in diabetic rats, at the same time the Tb.Sp is increased, together

Figure 1. Scheme of a distal rat femur in which are indicated the regions analysed using micro-CT, indicating its dimensions and distances from the reference (growth plate). The trabecular region starts at 1 mm from the growth plate to avoid the primary spongy tissue, while the cortical region starts at 4 mm to select a zone with few or no trabeculae



indicating a deterioration in the trabecular microarchitecture (Figure 2), their values not reaching statistically significant levels.

In the cortical region, although the diabetic group appears to have a reduction in the thickness of the cortical wall, this being determined through the transverse sections (Cs.Th) or assumed in the three-dimensional model (Ct.Th), this does not reach statistically significant levels (Table 3). The variables B.Ar, I and Ecc show very similar values in the two groups. The cortical regions of two representative samples can be seen in Figure 3.

Discussion

The study carried out shows that diabetic rats have a volumetric bone density similar to non-diabetic rats. However, differences are observed in the trabecular bone in the structural parameters. There is a reduction in BV/TV, a lower trabecular connectivity and a predominance of cylindrical trabeculae in the GK rats. The trabecular structural variables in which there are significant differences between the diabetic and control rats are those related to bone resistance. The lower quantity of bone indicated by the reduction in BV/TV, and the great loss of trabecular connectivity revealed by the increase in Tb.TPf in the diabetic group, result in an evident reduction in biomechanical resistance. In addition, it has been shown that the tube-like trabeculae, which predominate in the diabetic group, are less resistant to mechanical load than the plate-like trabeculae[12], more abundant in the control group, from which is deduced the SMI value. All these data indicate that, although their bone density is normal, the GK rats would have a lower biomechanical resistance, which could suggest that the higher prevalence of fractures which occurs in type 2 diabetes would be related to alterations in bone quality.

There are few studies carried out with this experimental model. Zhang et al. measured, in a group of GK rats, the bone mineral density using

Table 1. Volumetric bone mineral density in the trabecular an cortical regions of the distal femur of control and diabetic rats

	Rats WI control (average ± SD)	Rats GK diabetics (average ± SD)	Value of p
BMDv trabecular (mg/cm^3)	306.63 ± 48.78	261.23 ± 45.54	NS
BMDv cortical (mg/cm^3)	1,490.97 ± 227.57	1,727.13 ± 133.95	NS

SD: standard deviation. BMDv: volumetric bone mineral density. NS: not significant

Table 2. Results of the microstructural variables of the trabecular region of the distal femurs of control and diabetic rats

	Rats WI control (average ± SD)	Rats GK diabetics (average ± SD)	Value of p
BV/TV (%)	20.68 ± 2.87	15.51 ± 2.90	0.034
BS/BV (mm^{-1})	44.50 ± 9.21	47.76 ± 5.21	NS
BS/TV (mm^{-1})	9.10 ± 1.71	7.31 ± 0.88	NS
Tb.Th (µm)	84.15 ± 11.72	77.38 ± 5.83	NS
Tb.Sp (µm)	385.28 ± 103.73	332.18 ± 54.31	NS
Tb.N (mm^{-1})	2.47 ± 0.34	2.00 ± 0.30	NS
Tb.Pf (mm^{-1})	2.98 ± 2.58	10.01 ± 2.45	0.004
SMI	1.24,± 0.04	1.66 ± 0.18	0.001
DA	0.58 ± 0.06	0.55 ± 0.02	NS

SD: standard deviation. BV/TV: bone volumetric fraction. BS/BV: bone specific surface. BS/TV: bone specific density. Tb.Th: trabecular thickness. Tb.Sp: trabecular separation. Tb.N: trabecular number. Tb.Pf: trabecular pattern factor. SMI: structural model index. DA: degree of anisotropy

Table 3. Results of the microstructural variables of the cortical region of the distal femurs of control and diabetic rats

	Rats WI control (average ± SD)	Rats GK diabetics (average ± SD)	Value of p
B.Ar (mm^2)	5.78 ± 0.50	5.79 ±,0.32	NS
I (mm^4)	21.87 ± 5.09	21.11 ± 2.38	NS
Cs.Th (µm)	396.92 ± 23.23	373.61 ± 22.74	NS
Ct.Th (µm)	458.23 ± 15.40	433.07 ± 22.99	NS
Ecc	0.74 ± 0.03	0.79 ± 0.02	NS

SD: standard deviation. B.Ar. average transverse area of the bone. I: average polar inertial moment. CsTh: thickness of transverse section. CtTh: cortical thickness. Ecc: eccentricity

Figure 2. Three- dimentional representation of the trabecular region analysed in the distal femur of a representative sample of the control group and the diabetic group

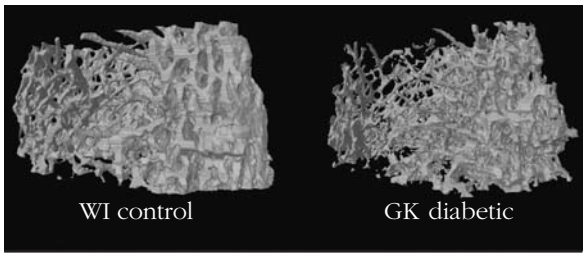
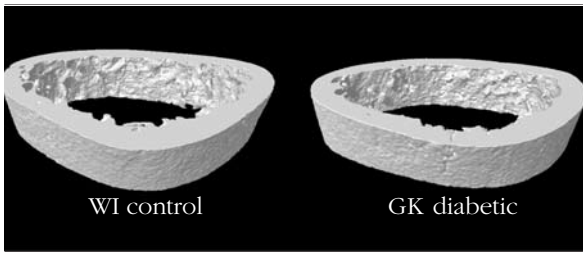


Figure 3. Three- dimentional representation of the cortical region analysed in the distal femur of a representative sample of the control group and the diabetic group



DXA and the microstructure with classic histomorphometric techniques in 2D[7]. These authors found a reduction in bone mass and a change in the histomorphometry with a decrease in BV/TV, similar to that found in our study. Ahmad et al., using peripheral quantitative computerised tomography (pQCT), observed a decrease in volumetric bone mineral density predominantly in the trabecular section[14]. The measurements were taken in the humerus, tibia and metatarsals of female rats, which could explain the differences observed from our results. In none of the regions analysed in this work were there found differences in the cortex. However, another work, using radiogrametric techniques in a group of 10 GK rats observed a decrease in cortical thickness in the metatarsal and humerus[15]. The data observed are heterogeneous, probably due to the different techniques used and the different places where measurements were taken. However, in all of them, trabecular affectation predominates and, when it was determined, a reduction in biomechanical bone resistance. Another model of non-obese diabetic rat is that of Zucker rats, developing the disease progressively until the serious complications of the disease appear. These rats show a decrease in bone mass, both cortical and trabecular, smaller sized large bones, and a deterioration in the biomechanical and microstructural properties of the cortical and trabecular bone[16,17].

Various mechanisms may explain this change. Glucose represents the principal source of energy to the osteoclasts, with hyperglycemia being responsible for an increase in osteoclast activity, with an increase in bone remodelling and a decrease in the quantity and quality of bone[2]. On the other hand, hyperglycemia provokes the non-enzymatic glycosylation of the bone proteins, damaging bone quality[18]. In turn, glycosuria increases hypercalciuria with changes to the PTH/vitamin D system. These deleterious effects on bone quality may be partially compensated for by an increase in bone mass associated with obesity[19]. An alteration in calcium metabolism may also contribute to the deterioration of bone quality. In diabetics an increase in calciuria has been described, which has been related to hyperglycemia and glycosuria. This provokes secondary hyperparathyroidism which exerts a prejudicial effect on the bone, especially on the trabecular section[20]. The alteration of the vitamin D and parathormone metabolism is particularly prominent in patients with reduced renal function. Microangiopathy can alter endothelial function[21], and macroangiopathy with arteriosclerosis can cause a reduction in blood supply to the bone[22,23]. On the other hand, in patients with neuropathy a change in the load on the bone can also contribute to the loss of bone mass. We can say, therefore, that there are multiple mechanisms which exert a deleterious effect on bone in experimental animals with type 2 diabetes which can explain the alteration in bone quality in these models.

In conclusion, we can say that Goto-Kakizaki rats are a valid model for the study of type 2 diabetes, since they eliminate a significant confusion factor, overweight. Although the sample size is small, we found a deterioration in the microstructure in the femoral trabeculae, with, however, the volumetric bone mineral density being preserved.

Bibliography

1. Olmos JM, Pérez Castrillón JL, García MT, Garrido JC, Amado JA, González Macías J. Bone densitometry and biochemical bone remodeling markers in type 1 diabetes mellitus. Bone Miner 1994;26:1-8.
2. Carnevale V, Romagnoli E, D'Erasmo E. Skeletal involvement in patients with diabetes mellitus. Diabetes Metab Res Rev 2004;20:196-204.
3. Cortés Sancho R, Pérez Castrillón JL, Martín Escudero JC, Iglesias S, Álvarez Manzanares P, Ramos R. Type 2 diabetes mellitus as a risk factor for hip fracture. J Am Geriatr Soc 2004;52:1778-9.
4. De Liefde II, Van der KM, De Laet CE, Van Daele PL, Hofman A, Pols HA. Bone mineral density and fracture risk in type-2 diabetes mellitus: The Rotterdam Study. Osteoporos Int 2005;16:1713-20.
5. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia 2005;48:1292-9.
6. Janghorbeni M, Van Dam RM, Willet L, Hu FB. Systematic review of type 1 and type 2 diabetes mellitus and risk of fracture. Am J Epidemiol 2007;166:495-505.
7. Zhang L, Liu Y, Wang D, Zhao X, Qiu Z, Ji H, Rong H. Bone biomechanical and histomorphometrical investment in type 2 diabetic Goto-Kakizaki rats. Acta Diabetol 2009;46:119-26.

8. Feldkamp LA, Davis LC, Kress JW. Practical cone-beam algorithm. J Opt Soc Am 1984;A6:612-19.
9. Xuan L, Sasov A. Cluster reconstruction strategies for micro CT and nano Ct scanners. In: Proceedings of the Fully Three-Dimensional Image Reconstruction Meeting in Radiology and Nuclear Medicine, July 6-9, 2005, Salt Lake City, UT, USA.
10. Hildebrand T, Rüegsegger P. A new method for the model independent assessment of thickness in three-dimensional images. J Microsc 1997;185:67-75.
11. Ulrich D, van Rietbergen B, Laib A, Rüegsegger P. The ability of three dimensional structural indices to reflect mechanical aspects of trabecular bone. Bone 1999;25:55-60.
12. Hildebrand T, Rüegsegger P. Quantification of bone microarchitecture with the structure model index. Comput Methods Biomech Biomed Eng 1997;1:15-23.
13. Hahn M, Vogel M, Pompesius-Kempa M, Delling G. Trabecular bone pattern factor: A new parameter for simple quantification of bone microarchitecture. Bone 1992;13:327-30.
14. Ahmad T, Ohlsson C, Sääf M, Östenson CG, Kreicbergs A. Skeletal changes in type-2 diabetic Goto-Kakizaki rats. J Endocrinol 2003;178:111-6.
15. Östenson CG, Fière V, Ahmed M, Lindström P, Brismar K, Brismar T, et al. Decreased cortical bone thickness in spontaneously non-insulin-dependent diabetic GK rats. J Diabetes Complications 1997;6:319-22.
16. Prisby RD, Swift JM, Bloomfield SA, Hogan HA, Delp MD. Altered bone mass, geometry and mechanical properties during the development and progression of type 2 diabetes in the Zucker diabetic fatty rat. J Endocrinol 2008;199:379-88.
17. Reinwald S, Peterson RG, Allen MR, Burr DB. Skeletal changes associated with the onset of type diabetes in the ZDF and ZDSD rodent models. Am J Physiol Endocrinol Metab 2009;296:E765-74.
18. Yamagishi S, Nakamura K, Inoue H. Possible participation of advanced glycation end products in the pathogenesis of osteoporosis in diabetic patients. Med Hypotheses 2005;65:1013-5.
19. Pérez Castrillón JL, De Luis D, Martín Escudero JC, Asensio T, Del Amo R, Izaola O. Non-insulin-dependent diabetes, bone mineral density, and cardiovascular risk factors. J Diabetes Complications 2004;18:317-21.
20. Hofbauer LC, Brueck C, Singh SK, Dobnig H. Osteoporosis in patients with diabetes mellitus. J Bone Miner Res 2007;22:1317-28.
21. Sanada M, Taguchi A, Higashi Y, Tsuda M, Kodama I, Yoshizumi M, et al. Forearm endothelial function and bone mineral loss in postmenopausal women. Atherosclerosis 2004;176:387-92.
22. McNair P, Christensen MS, Christiansen C, Madsbad S, Transbøl I. Is diabetic osteoporosis due to microangiopathy? Lancet 1981;1(8232):1271.
23. Vogt MT, Cauley JA, Kuller LH, Nevitt MC. Bone mineral density and blood flow to the lower extremities: The study of osteoporotic fractures. J Bone Miner Res 1997;12:283-9.

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Diagnostic challenges in the phosphorus calcium metabolism in a female patient

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Summary
We present the case of a female patient who had an intervention in a cervical nodule in the context of moderate hypercalcemia, with a histological diagnosis of a possible parathyroid carcinoma, whose later development made it necessary to rethink the diagnosis.

Key words: *moderate hypercalcemia, osteitis fibrosa cystica, primary hyperparathryoidism.*

Introduction
Primary hyperparathyroidism is being diagnosed earlier and earlier due to the routine testing for calcemia. Light hypercalcemia is its most frequent characteristic, and osteoporosis predominantly affecting cortical bone, is the most common finding in the bone. On the other hand, the typical skeletal affectation of this disease, osteitis fibrosa cystica, is nowadays exceptional. For this reason, the presentation of the classic skeletal manifestations of hyperparathyroidism may lead to doubts and diagnostic errors in clinics today.

Clinical case
A woman of 49 years of age, without personal or family history of interest, except an episode of renal lithiasis two years previously, who attended a primary care clinic due to the cardinal symptoms of diabetes of a year's development (polyuria, polydipsia and discrete non-quantified ponderal loss). An analysis was carried out, with the following results: baseline glycemia, 130 mg/dl; calcium, 12 mg/dl (normal values: 8.5-10.5); total alkaline phosphatase, 2,260 U/l (normal values: 98-279); for which reason she was referred to the surgical service for an evaluation of hypercalcemia. Notable in the physical examination was a cervical nodule adhering to deep layers, with growth towards the mediastinum. An X-ray was carried out with technetium sestamibi, which showed capture in the lower right parathyroid gland, which was the reason for deciding to intervene, with the suspicion of parathyroid cancer. A hemithyroidectomy was carried out on the right hand side and the extirpation of the lower right parathyroid, with resulting anatomopathological neoplasms secreting parathormone (PTH) with the phenomenon of vascular microinvasion of low proliferative activity, alongside unchanged thyroid tissue.

After the intervention the patient was referred to the endocrinology service for follow up. At this point the patient complied with the criteria for obesity (weight: 83 kg, height: 1.54 m, BMI: 35 kg/m^2), and presented, in addition, type 2 diabetes

of a year's development since diagnosis, in treatment with diet and exercise. In carrying out an anamneses the patient only reported mechanical pain in the lower limbs and thorax, and tumoration on the right tibia of some months development, which had been examined through conventional X-ray and was waiting for a diagnostic biopsy (Figure 1). The study was completed with X-rays in other locations (Figure 2). After the intervention, various complementary tests were carried out, with the following results: basic biochemistry, normal, except for hyperglycemia of 144 mg/dl; calcemia, 8.8 mg/dl (normal values 8.5-10.5); phosphorus, 4 mg/dl (normal values: 2.5-5); elevated levels of markers for bone remodelling: total alkaline phosphatase, 313 U/l (normal values: 98-279), bone alkaline phosphatase, 62.1 µg/ml (normal values: 7.5-33.7). The thyroid function was compatible with subclinical hypothyroidism, with TSH of 4.4 mUI/ml ().4-4); raised levels of intact PTH (103 pmol/l; normal values 29-85); 24 hour calciuria, normal; glycosylated haemoglobin (HbA1c); 5.5%; and urinary albumin excretion, negative.

Also carried out were: thyroid echography, which showed a solid mass of 22 mm located in the left parathyroid compatible with a recurrent tumour; bone gammagraphy, with intense capture in the distal third of the right tibia and of lower intensity in other locations. Bone densitometry with femoral T-score values of -3.1 and lumbar T-score of -0.8, compatible with cortical osteoporosis.

Given that the benign development of the symptoms are not particularly compatible with the initial diagnosis of parathyroid carcinoma and the presence of the bone lesion, the anatomopathaological study of the intervention was reviewed jointly with the biopsy of the tibial tumour, with the final result of possible osteitis fibrosa cystica associated with parathyroid adenoma. Subsequently, the patient maintained normal levels of calcemia, with slightly raised levels of intact PTH, sufficient metabolic control of her diabetes with diet and exercise and normal thyroid function. There was an intervention in the right tibial tumour with anatomopathological results of areas of fibrosis and trabecular thinning related to osteoporosis. In a later echographic check the size of the parathyroid lesion had reduced, for which reason a conservative approach was maintained. During the follow up the patient remained asymptomatic with improvement in the bone lesions, and analytical checks and cervical examinations were maintained, with no changes over a period of 6 years. In the follow up, a malignant tumour of gynaecological origin was diagnosed, for which treatment with chemotherapy with cisplatin and radiotherapy were initiated. Subsequently, the patient had an episode of peribuccal paresthesia and tetany, with hypocalcemia being confirmed by various analytical test, resulting in the carrying out of a new study of the phosphorus calcium metabolism, with the following results: calcium, 6.2 mg/dl (normal values: 8.6-1.2); phosphorus, 3.3 mg/dl (normal values 2.5-5); magnesium, 0.8 mg/dl (normal values: 1.8-2.6); 25 OH vitamin D, 23.2 ng/ml; hepatic and renal functions unaltered. After assessing different possibilities, a diagnosis was established of functional hyperparathyroidism due to secondary hypomagnesemia resulting from the chemotherapy, and treatment with oral magnesium supplements was initiated, with a good clinical and analytical response.

Discussion

The diagnosis of primary hyperparathyroidism now occurs earlier and earlier due to the carrying out of routine analysis for calcemia, which means that the skeletal affectation typical of this disease, osteitis cystica fibrosa, is becoming ever less frequent. The bone affectation most commonly associated with hyperparathyroidism currently is osteoporosis, with fundamentally cortical affectation[1]. In both entities remineralisation usually happens after treatment for the adenoma[2-3].

The typical analytical profile of primary hyperparathyroidism is raised levels of blood calcium, parathormone, alkaline phosphatase and calciuria, with levels of phosphorus normal or low. An increase in markers for bone remodelling is also observed, of variable duration after surgery[4]. It has been reported that between 11% and 40% of patients having interventions for primary hyperparathyroidism maintain raised levels of PTH during subsequent follow up, despite a normalisation of levels of calcium. Although the pathogeny of this phenomenon has not been well clarified, various theories have been proposed. Thus, the persistence of raised levels of PTH after surgery could be a transitory compensatory response which would favour bone mineralisation[5]. Other authors have described the presence of alterations in renal function as the cause of the raised PTH[6], although later studies do not confirm this finding[7]. The presence of low levels of vitamin D, a frequent finding in different groups in the population should also be considered[8].

Persistent hyperparathyroidism can produce severe skeletal deformities and haemorrhage, which form lytic lesions called "brown tumours" due to the deposit of haemosiderin in their interiors[9]. In the majority of cases, the diagnosis of these lesions occurs in patients previously diagnosed with hyperparathyroidism, although on occasions it may be the first manifestation of the disease. The differential diagnosis of this lesion with other bone lesions, such as osteoclastoma, may raise difficulties, although recent advances in the field of immunohistochemistry facilitates its diagnosis[10].

Parathyroid carcinoma is an infrequent disease, with an estimated frequency of 2.1% of cases of hyperparathyroidism[11]. Among its clinical manifestations are a marked hypercalcemia, above 14 mg/dl in the majority of cases, and levels of PTH 5 to 10 times higher than normal[12]. As with other endocrine tumours, it is difficult to establish the malignant nature of the lesion from histological findings. The typical anatomopathological characteristics include a lobular pattern separated by

Figure 1. Lesion in tibia suggestive of osteoclastoma

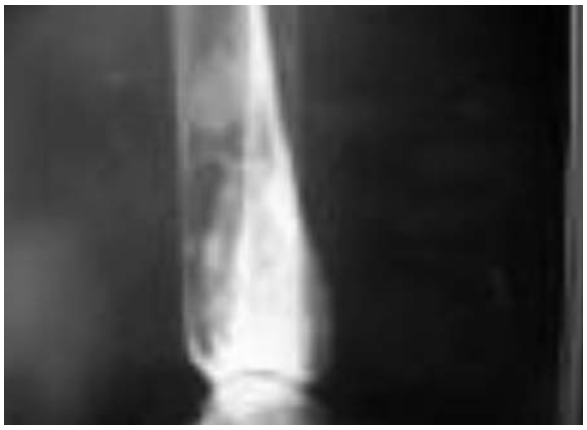
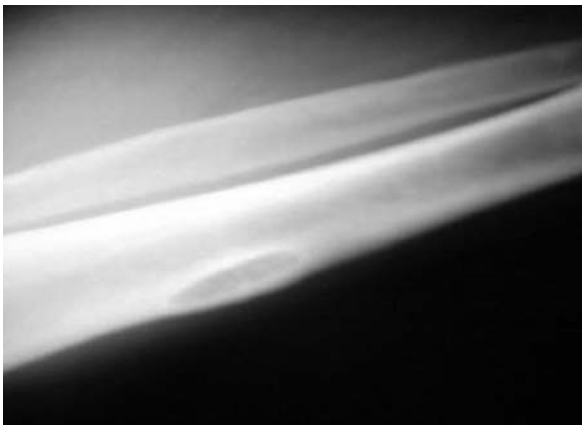


Figure 2. Radiography of forearm which shows cortical lesion



fibrous trabeculae, a high degree of mitosis and invasion of the capsules and blood vessels, although these may also be found in some adenomas. In this case, the moderately raised levels of calcium and intact PTH, their normalisation after surgery, and its later asymptomatic course, made necessary a rethink of the initial anatomopathological diagnosis.

Finally, hypocalcemia is frequent in those patients receiving treatment with cisplatin. In the case of hypomagnesemic hypocalcemia is appears to be the result of a reduction in the secretion of PTH, as well as a higher resistance to its action in the bone and kidney, both caused by hypomagnesemia by means of a complex mechanism which is not totally understood[13]. Although oral supplements appear to be efficacious in the development of hypomagnesemia associated with cisplatin, it does not offer complete protection against the development of this situation.

The singularity of our case is found in the infrequency of the diagnosis of primary hyperparathyroidism with the presence of bone lesions, as well as the development of hypomagnesemic hypocalcemia as a secondary effect of the treatment with cisplatin. In conclusion, we can say that, although its incidence has diminished due to early diagnosis of hyperparathyroidism, osteitis fibrosa cystica should be included in the differential diagnosis of bone lesions. Given that the typical anatomopathological characteristics of parathyroid carcinoma may be found in some cases of adenoma, the initial clinical manifestations and the evolutionary course of the condition may assist in the differential diagnosis. In addition, in patients in treatment with cisplatin analytical checks should probably be carried out to detect the presence of hypomagnesemia and other disorders, such as hypocalcemia

Bibliography

1. Parisien M, Silverberg SJ, Shane E, Dempter DW, Bilezikian JP. Bone disease in primary hyperparathyroidism. Endocrinol Metab Clin North Am 1990;19:19-34.
2. Silverberg SJ, Gartenberg F, Jacobs TP, Shane E, Siris E, Staron RB, et al. Increased bone mineral density after parathyroidectomy in primary hiperparathyroidism. J Clin Endocrinol Metab 1995;80:729-34.
3. Kulak CA, Bandeira C, Voss D, Sobieszczyk SM, Silverberg SJ, Bandeira F, et al. Marked improvement in bone mass after parathyroidectomy in ostitis fibrosa cystica. J Clin Endocrinol Metab 1998;83:732-5.
4. Seibel MJ, Gartenberg F, Silverberg SJ, Ratcliffe A, Robins SP, Bilezikian JP. Urinary hydroxypyridinium cross-links of collagen in primary hyperparathyroidism. J Clin Endocrinol Metab 1992;74:481-6.
5. Mandal AK, Udelsman R. Secondary hyperparathyroidism is an expected consecuence of parathyroidectomy for primary hyperparathyroidism: a prospective study. Surgery 1998;124:1021-7.
6. Lundgren E, Rastad J, Ridefelt P, Juhlin C, Akerstrom G, Ljunghall S. Long term effects of parathyroid operation on serum calcium and parathyroid levels in sporadic primary hyperparathyroidism. Surgery 1992;112:1123-9.
7. Westerdahl J, Valdemarsson S, Lindblom P, Bergenfelz A. Postoperative elevated serum levels of intact parathyroid hormone after surgery for parathyroid adenoma: signs of bone remineralization and decreased calcium absorption. World J Surg 2000;24:1323-9.
8. Holick MF. Vitamin D deficiency. N Engl J Med 2007; 357:266-81.
9. Neyser JS, Postma GN. Brown tumor of the mandibule. Am J Otolaryngol 1996;17:407-9.
10. Guenther R, Krenn V, Morawietz L, Dankof A, Melcher I, Schaser KD, et al. Giant cell tumors of the bone: molecular profiling and expression analysis of Ephrin A1 receptor, Claudin 7, CD52, FGFR3 and AMFR. Pathol Res Pract 2005;201:649-63.
11. Obara T, Fujimoto Y. Diagnosis and treatment of patients with parathyroid carcinoma: An update and review. World J Surg 1991;15:738-44.
12. Wynne AG, van Herdeen J, Carney JA, Fizpatrick LA. Parathyroid carcinoma: Clinical and patologic features in 43 patients. Medicine 1992;71:197-205.
13. Rude RK. Magnesium metabolism and deficiency. Endocrinol Metab Clin North Am 1993;22:377-95.

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Bone metabolism regulation through RANK-RANKL-OPG system

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Summary

Osteoporosis is a disorder in which loss of bone strength leads to fragility fractures. The discovery of osteoprotegerin (OPG) and the receptor activator of nuclear factor-κβ ligand (RANKL) as final effector in osteoporosis pathogenesis have lead to a better understanding of bone remodelling. When RANKL binds to its natural receptor (RANK), osteoclastic differentiation and activation is initiated. OPG is a decoy receptor that binds to RANKL and prevents its osteoclastogenic effect.

Key words: *postmenopausal osteoporosis, osteoprotegerine, RANKL.*

Introduction

According to the definition proposed in 2001 by the National Institutes of Health (NIH) of the US, osteoporosis (OP) is a skeletal disorder characterised by a reduction in bone resistance which predisposes it to a high risk of fractures[1]. In Spain it has been estimated that approximately 13% of the female population has OP in the lumbar spine or in the femoral neck, these figures increasing to 26% in women over 50 years of age[2]. The prevalence in women is three times that in men[3].

The most significant clinical problems of OP are fractures and their complications. The fractures may develop towards a complete recuperation, or, on the contrary, be the cause of chronic pain, disability or even to an increase in mortality[4]. For hip fractures, this mortality has been estimated at 10-20% in one year[5]. In addition to this impact on the individual, osteoporotic fractures have significant repercussions on society, since they result in high health costs related to an increase in medical appointments, hospital admissions or in admissions into older peoples' residential homes[5].

Given the importance and the implications of this disease in the modern world, knowledge of its pathogenesis would support the development of its prevention and treatment. For this reason, this article will review this pathogenesis at some

length, starting with the process of bone remodelling and how this overlaps with mechanical processes and endocrine and local factors until it arrives at the final effector most recently described: the RANK/RANKL/OPG system.

Classical theory of bone remodelling

Bone fragility may be the result of a failure in the formation of bone, of an excess resorption or of inadequate formation of bone in response to an increase in resorption[6]. Bone remodelling is the physiological mechanism by which adult bone renews itself constantly by the activation of the basic multicellular units (BSUs), with the aim of repairing the microfissures caused by fatigue, and to maintain intact its structure and function[7]. The BSUs make up, morphologically and functionally, the bone tissue. They contain all the elements necessary for its remodelling, and act in an integrated and sequential way with the participation of the osteoclasts (derived from haematopoietic cells of monocyte-macrophage lineage) and the osteoblasts (of mesenquimal origin). The osteocyte, on its part, is a cell which is capable of activating osteoclasts or osteoblasts in response to antagonistic stimuli as a function of the local load. There are various theories about what the stimulus is which activates the osteocytes. It seems that the most commonly accepted theory would be that proposed by Parfitt[8], which suggests that the stimulus is produced by the movement of the fluid in the fibres which anchor the osteocyte to the bone walls in the canaliculi[9].

Each BSU, of which there can be a million functioning at any moment, starts its work at a set time and place, directing itself towards the area of bone which needs to be replaced[7]. To do this, it advances across the trabecular surface excavating and replacing the tissue. The cellular components of the BSUs, osteoclasts and osteoblasts act in an orchestrated fashion, completing each remodelling cycle[10]. The cycle (Figure 1) starts with the activation, by unknown mechanisms, of the bone surface in repose, which attracts from the bloodstream the pre-osteoclasts, precursors of the osteoclasts. The resorptive phase is initiated with the formation of the so-called Howship lacunae or resorption pits, and end with the apoptosis of the osteoclasts. The process of destruction is more rapid than that of regeneration, which means that any increase in the rhythm of remodelling will result in a loss of bone mass. Similarly, an excess of resorption may produce loss of trabecular structures, leaving the bone without a pattern for the new formation of bone[6].

As a consequence of bone remodelling, a number of biochemical markers for bone remodelling (MBR) are released, which show us in an indirect way the state of this formation/resorption process. An increase in products of resorption will indicate an accelerated bone turnover, showing a negative balance in the remodelling with an increase in bone loss. Thanks to these indirect markers it is possible to diagnose clinically and non-invasively the metabolic status of bone. Of these, those most used are the C and N telopeptides, which are terminal sections of the triple helix of type 1 collagen: one of these ends with carbon (C-telopeptide –CTx-) and the other two with nitrogen (N-telopeptide –NTx-). Due to their low molecular weight they are eliminated in the urine, from which we can determine their levels. In spite of this, nowadays most clinical studies determine the levels of the markers in the peripheral blood.

Initial role of bone mechanostat

The term mechanostat refers to the model proposed by Harold Frost[11] to explain the pathogenic mechanism by which the growth and loss of bone is regulated as a function of the mechanical stimulus which deforms it locally (force, pressure, torsion). According to this model, an increase in muscular force exerted on the bone (during growth or in response to an increase in load) or a reduction in load (through inactivity or immobilisation) will affect its mass, size and resistance in a positive or negative way, respectively. Thus through mechanical stimulus a system of feedback is put into action, which would determine when the bone needs more resistance or when it is not necessary[12].

Hence, the theory of mechanostat would explain how the mechanical load applied to the bone acts by setting in motion a complex process of bone remodelling, in which the osteocyte plays a fundamental role as mechanosensor, which transforms the mechanical signal in to a chemical one, which, in turn, produces the osteoblast/osteoclast response.

However, bones are essentially biomechanical. Remodelling is regulated by factors which are local and systemic: the process of adaptation of bone to load is not explained solely by a mechanical effect, but also depends on genetic-familial factors (most of the bone mass of an individual depends on their genetics) and on the normal state of the cells involved, on local-regional neurovascular factors, the endocrine-metabolic environment of the organism and the local environment of the bone[7,13]. Hence, the bone remodelling mechanism is modulated by both mechanical and non-mechanical factors (Table 1); among the latter, the most important are local factors, autocrines and paracrines, as well as endocrine-metabolic factors.

Hormonal regulation of bone metabolism

Among the non-mechanical factors involved in the metabolism of bone, the hormones play a primordial role. Hormonal regulation of the phosphorus-calcium metabolism is carried out through three principal hormones: parathyroid hormone (PTH), 1,25 colecacliferol (active metabolite of vitamin D_3) (Figure 2) and, to a lesser extent, calcitonin and four more hormones: growth hormone (GH), thyroxine, glucocorticoids and sexual steroids. Below, we briefly review the role of each of these.

1. PTH (parathyroid hormone), produced in the parathyroid glands, it is the hypercalcemic

hormone par excellence. It carries out its action at 3 levels: directly on the bone, stimulating the osteoclasts and favouring bone resorption, an action linked to the presence of vitamin D; in the kidney, increasing the distal tubular resorption of calcium; and indirectly on the intestine, stimulating the synthesis of 1,25 OH calciferol which, in turn, increases the absorption of calcium.

2. Calcitonin, produced in the C cells of the thyroid, acts directly on the osteoclast receptors. Its physiological role is controversial. It has been shown that in situations in which there is an increase in its secretion (carcinoma of the thyroid medullar) or in which there is an absence of C cells (total thryoidectomy) calcemia remains at normal levels and there are no changes in the bone[14]. However, at pharmacological doses, calcitonin possesses an inhibitory effect on bone resorption by reducing the number and activity of the osteoclasts, which means that it may be considered to be a hormone which is protective of bone tissue[15].

3. Vitamin D_3 is provided very scarcely through food, or is synthesised in the skin thanks to the action of ultraviolet solar radiation. It is transformed into 25 (OH) colecalciferol (calcidiol) in the liver and into 1,25 (OH) colecacliferol (calcitriol) in the kidney, biologically active forms. The principal action of vitamin D occurs in the small intestine, favouring the absorption of dietary calcium. In the bone it acts, in the presence of PTH, to stimulate the differentiation of the osteoclasts, and therefore, bone resorption, making possible adequate mineralisation. In the kidney it increases the proximal tubular resorption of calcium. A deficit or insufficiency of vitamin D_3, such as occurs in postmenopausal women, carries an increased risk of secondary hyperparathyroidism with the object of maintaining normocalcemia and an associated loss of bone mass.

4. Today, it is considered that GH (growth hormone) is synthesised, in addition to in the hypophysis, in other cells of the organism, including in the osteoblasts. Thus it is considered to have an endocrine, as well as a paracrine, effect[16]. GH acts directly on the osteoblast receptors, stimulating their activity, which produces an increase in the synthesis of collagen, osteocalcin, and alkaline phosphatase. It also acts indirectly by increasing the synthesis of insulin-like growth factors I and II (IGF-I and IGF-II) by the osteoblasts, which favours their proliferation and differentiation.

Figure 1. Phases of bone remodelling

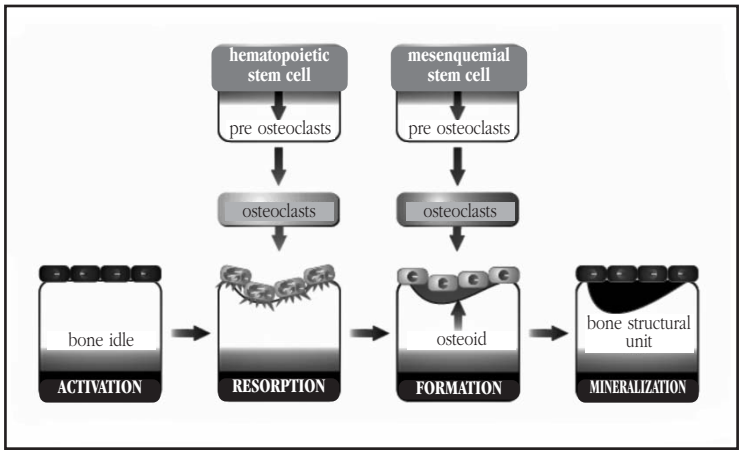
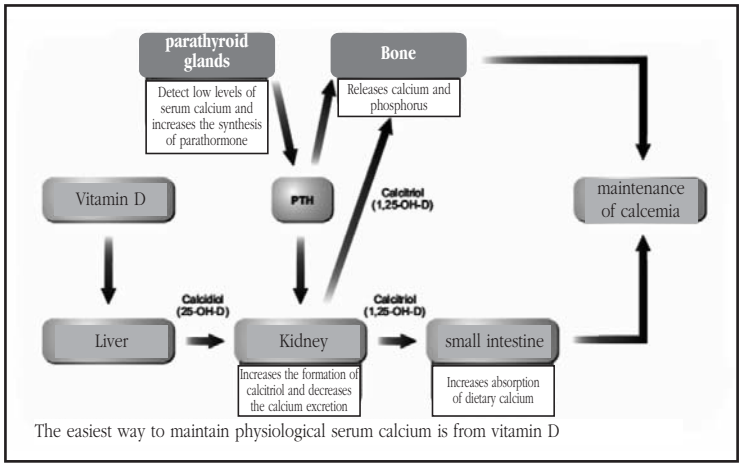


Figure 2. Regulation of phosphorus-calcium metabolism by PTH and vitamin D



5. The thyroid hormones are essentially hypercalcemics. In the bone, they act to stimulate the osteoclasts which accelerates the speed of bone turnover. Thus hyperparathyroidism brings with it the risk of OP.

6. The glucocorticoids act physiologically as modulators of bone remodelling. At pharmaceutical doses they diminish the activity of the osteoblasts and induce bone loss, leading to secondary OP, an action mediated in part by PTH and 1,25 OH colecalciferol.

7. The sex hormones play a significant role in bone. Until a few years ago it was thought that the fundamental role of the oestrogens in the maintenance of bone mass was the consequence of their interaction at all levels through the interleukine loop; generally, they inhibit resorption and stimulate the formation of bone. The oestrogens act on the osteoblasts directly, modulating their proliferation and differentiation, and increasing the secretion of the cytokines which, in turn, would act as a paracrine, stimulating or inhibiting the activity of the osteoclasts. On the other hand, they also have a direct effect on the osteoclasts in modulating

Table 1. Mechanical and non-mechanical factors related to the process of bone remodelling

Mechanical	Non-mechanical
• Gravitational force	• Hormones
• Weight of an individual	• Local factors (autocrines/paracrines)
• Physical activity-sedentariness	• Age/sex/genetics
• Muscular contractility	• Diet (calcium, vitamins, minerals...)
• Effort	• Work occupation/ergonomics
• Prolonged weightlessness-bedrest	• Some diseases (e.g. rheumatoid arthritis)

their activity (Figure 3)[17]. More recently it has been confirmed that the oestrogens can increase levels of osteoprotegerin (OPG), a protein which inhibits resorption produced by the osteoblasts, and because of which, could play a significant role in the regulation of osteoclastogenesis[15]. This activity would explain the loss of bone linked to hypoestrogenism after the menopause. For their part, the androgens have a fundamentally anabolic effect, in way which facilitates osteoblast action and inhibits bone resorption by diminishing the secretion of cytokines such as IL-6[18].

Local regulatory factors for bone remodelling

One of the most significant conceptual advances in the 1980s was the recognition of the regulatory role of many cytokines in the physiopathological regulation of bone resorption[19]. Currently it is known that bone contains cells which can produce prostaglandins, nitric oxide, growth factors, as well as cytokines, whose interactions are complex[20]. These substances, synthesized by the bone cells or coming from the medullar microenvironment, act in an autocrine or paracrine fashion, modulating bone remodelling[12]. Table 2 schematises the principal local factors and their principal action on bone formation or resorption.

Cytokines and growth factors

The cytokines are polypeptides synthesised in lymphocyte or monocyte cells whose role includes various cellular functions, such as the immunological response, inflammation and haematopoiesis. The growth factors are polypeptides originating in cells inside or outside the bone which act essentially on cell growth, differentiation and proliferation.

In the bone, those polypeptides act to increase the proliferation and differentiation of the preosteoclasts (resorptive action), in some cases (IL-1, GM-CSF, etc). This would immediately lead to the formation of active osteoclasts which favour bone resorption. In other cases, the growth factors act to stimulate the formation of bone, since they stimulate the differentiation of the osteoblasts (for example, TGB-β) or increase the number and function of these cells (IGF-I and II) and their consequent reparative action.

Convergence theory: the RANK-RANKL-OPG system

The remodelling of bone is responsible for the combined action of the osteoclasts and the osteoblasts in a sequential and antagonistic though independent action, both stimulatory and modulatory due to different factors (mechanical, hormonal, local). It has only been since the end of the 1990s that the final effects of the whole of this process has been known: the receptor activator of nuclear factor kappa β ligand (RANKL), its natural receptor (RANK) and osteoprotegerin (OPG), all belonging to the family of tumour necrosis factors (TNF). RANKL is a protein expressed by the osteoblasts and their precursors under the control of hormones, cytokines and pro-resorptive growth factors. The bonding of RANKL to its natural receptor on the cell surface of the osteoclasts and their precursors, RANK, stimulates the fusion of the pre-osteoclasts, promoting the adherence of the osteoclasts to the bone, activating their function and increasing their survival by avoiding apoptosis[21,22]. OPG is, in turn, a protein synthesised by the osteoblasts and the stromal cells, which acts as a dummy receptor, blocking the bonding of RANKL with its natural receptor RANK. In this way, OPG blocks every one of the actions of RANKL, producing a reduction in the number of osteoclasts and thus increasing their apoptosis[22,23] (Figure 4).

Taking into account the antagonistic effects of the RANKL and OPG proteins, it is easy to understand that bone remodelling depends ultimately on the balance between them, which, in turn, is influenced by the many factors which we have reviewed up to this point. Thus the “convergence

theory" considers that the RANK/RANKL/OPG system is the final effector of most of the regulatory factors for bone remodelling (Figure 5)[19].

The osteoclasts, as has already been said, are derived from mononuclear precursors from the monocyte-macrophage line. Their differentiation into mature osteoclasts requires the expression of the macrophage colony-stimulating factor (M-CSF) or the stromal osteoblasts, in a synergistic action. In addition, the completion of the process of differentiation requires the expression of RANKL by the osteoblasts, and of RANK by the osteoclast precursors. The osteocytes would regulate the recruitment and function of the osteoclasts, inducing the expression of RANKL by the osteoblast cells. The osteoclasts, in turn, are capable of regulating, positively or negatively the functions of the osteoblasts[23].

On their part, the hormones, the cytokines and the growth factors would act on receptors in the osteoblasts and other cells to induce the production of RANKL. Some of these factors also suppress the production of OPG by the osteoblasts, increasing the RANKL/OPG ratio. In this situation, the free RANKL acts on the osteoclast precursors (M-CFU), increasing their function and maturation, and also on the mature osteoclasts, increasing their activity and protecting them from apoptosis.

In addition to PTH, other proresorptive agents which regulate the expression of RANKL or OPG include the interleukins IL-1, IL-7 and IL-17; TNFα, glucocorticoids and vitamin D. On the other hand many molecules which inhibit bone resorption, such as the oestrogens, IFNγ, TGFβ and the interleukins IL-4 and IL-13, have also been shown to regulated the RANKL/OPG balance (Table 3).

The main physiological role of the RANK/RANKL/OPG system is the regulation of bone remodelling, involved in a wide range of bone diseases in which an imbalance occurs between formation and resorption[24]. In addition, other functions outside the skeleton related to vascular calcification, the immune system and the development of the mammary glands have been confirmed in animal models[25]. Mutations

Table 2. Principal local regulatory factors of bone remodelling (adapted from[16,20])

		Stimulus of resorption	Inhibition of resorption	Increase in formation
Cytokines				
Interleukins	IL-1	+		
	IL-4		+	
	IL-6	+		
	IL-11	+		
Tumour necrosis factors	TNF-α	+		
Colony stimulating factor	GM-CSF	+		
	M-CSF	+		
Interferón γ	IFN-γ		+	
Prostaglandins	PGE	+		
Growth factors				
Insulin-type	IGF-I y II			+
Transformer	TGF-β			+
Fibroblastic	FGF	+		
Derivatives of platelets	PDGF	+		
Bone morphogenic proteins	BMPs			+
Leukotrienes		+		
Nitric oxide	NO			+

Figure 3. Molecular and cellular actions of the oestrogens in the regulation of bone remodelling (adapted from Riggs[18])

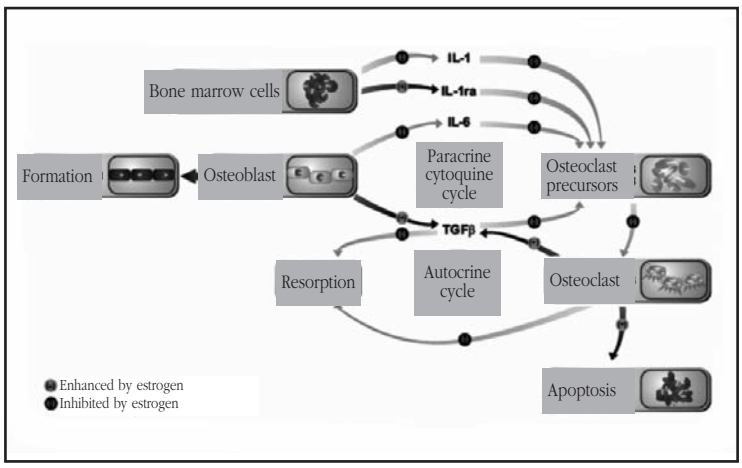


Figure 4. Regulation of osteoclastogenesis by the RANKL/RANK system: the RANK ligand bonds with its RANK receptor provoking the maturation of the pre-fusion osteoclasts into multinuclear osteoclasts and, finally, into activated osteoclasts

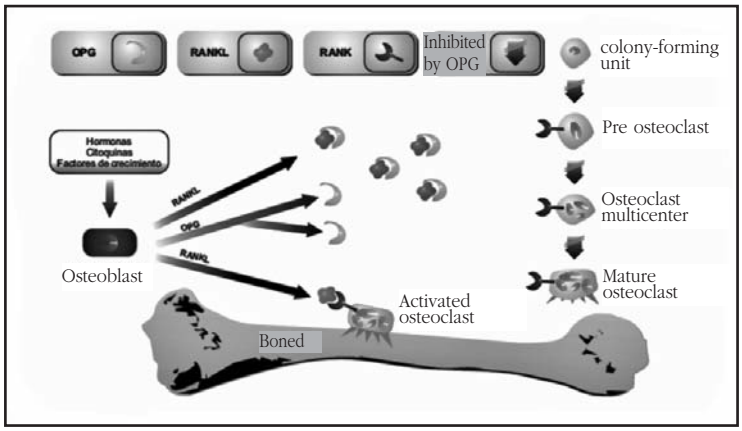
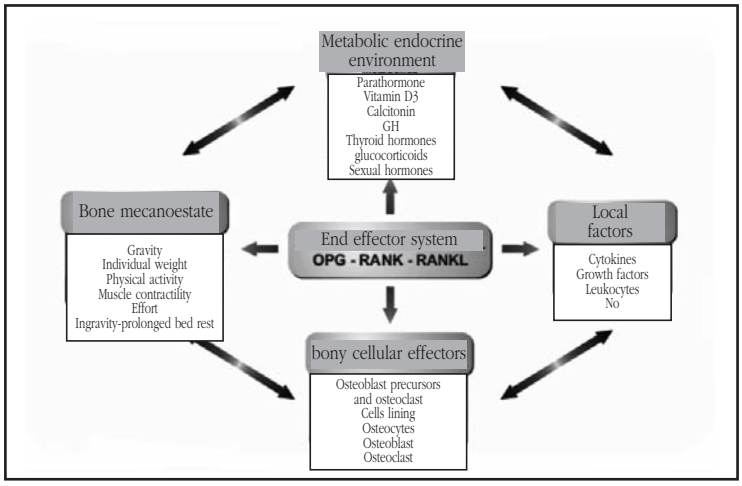


Figure 5. Convergence theory: confluence of modulatory factors of bone remodelling in the final effector system (adapted from Fiter[19])



have been identified in the genes for RANKL and OPG (and for their intracellular transporters) in diseases characterised by local alterations in bone remodelling, such as Paget's disease[26]. In animal models for rheumatoid arthritis, an early activation of RANKL and a suppression of OPG has been observed in inflamed joints[27]. It has also been seen that the cancerous cells in bone metastasis are capable of increasing the RANKL/OPG *ratio*, which stimulates bone resorption and makes available to the cancerous cells the space to grow within the bone. The same thing occurs with multiple myeloma, whose cells are even more destructive for bone[25]. The participation of the RANK/RANKL/OPG system in all these processes could have different clinical implications[25]:

- In prostate cancer OPG could be a new indicator for the diagnosis and early progression of the disease. In addition, given that those patients with prostate cancer who respond to antiandrogenic therapy have significantly lower levels of OPG, it could become a useful marker in the treatment of these patients. In addition, denosumab (AMG 162) (DMAB), an anti-RANKL monoclonal antibody, has been shown to increase bone mineral density and to reduce the incidence of new vertebral fractures in patients with prostate cancer who are receiving antiandrogenic therapy[28].

- Different studies have found that patients with multiple myeloma have lower concentrations of OPG than controls. Denosumab has shown persistent antiresorptive effects in patients with multiple myeloma and with bone metastasis from breast cancer[29].

- It is also possible that OPG participates in the pathogenesis of bone loss associated with chronic renal disease, and that which occurs after a solid organ transplant. However, as far as we know, the therapeutic possibilities of this participation by the RANK/RANKL/OPG system have not yet been explored.

- As has been commented on earlier, the RANK/RANKL/OPG system also plays a significant role in rheumatoid arthritis. Various randomised clinical trials with denosumab have shown the therapeutic usefulness of this anti-RANKL antibody in patients with rheumatoid arthritis which is not just limited to a reduction in bone loss, but also protection against bone erosion and structural damage[30,31,32].

- Finally, the aspect most investigated has been the aforementioned role of the RANK/RANKL/OPG system in postmenopausal osteoporosis. Thus, from the therapeutic point of view, it should be mentioned that denosumab has been authorized both by the America and European health authorities for this indication. The clinical data which endorse the utility of denosumab in the treatment of postmenopausal osteoporosis are reviewed in another article.

Final comments

Bone metabolism involves a series of phenomena much more complex than the simple interaction between a cell destructive of bone and one which forms new material as turnover, as was thought some decades ago. Thus, bone remodelling depends on many processes, not only cellular, but also endocrines of various kinds (oestrogens, vitamin D, PTH, calcitonin, even corticoids...), as well as auto- and paracrines with various growth factors, interleukins and leukotrienes, among others, which together with a true bone mechanostat, all come together in a final common effector system

which regulates the equilibrium between formation and resorption, which is the RANK-RANKL-OPG system.

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Bibliography

1. NIH Consensus Development Panel. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;285:785-95.
2. Díaz Curiel M, García JJ, Carrasco JL, Honorato J, Pérez Cano R, Rapado A, et al. Prevalencia de osteoporosis determinada por densitometría en la población femenina española. Med Clin (Barc) 2001;116:86-8.
3. National Osteoporosis Foundation. America's Bone Health. The State of Osteoporosis and Low Bone Mass. [Citado el 3 de septiembre de 2009]. Disponible en: www.nof.org/advocacy/prevalence.
4. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation, Washington, 2008.
5. US Department of Health and Human Services. Bone health and osteoporosis: a report of the surgeon general. Rockville, MD. US Department of Health and Human Services, Office of the Surgeon General, 2004. [Citado el 3 de septiembre de 2009]. Disponible en: www.hhs.gov/surgeongeneral/library/bonehealth/.
6. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. Clin Invest 2005;115:3318-25.
7. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev 2000;21:115-37.
8. Parfitt AM. Osteocytes. The link between strain, structure and strenght. En: ASBMR. 26th Annual Meeting Webcast. Plenary Symposium II. New insights into bone strenght. Harold M. Frost memorial session. Citado el 06.09. 2009. Disponible en:http://app2.capitalreach.com/esp1204/servlet/tc?cn=asbmr&c=10169&s=20282&e=3345&&. 2004.
9. Cano J, Campo J, Sánchez J, Bascones A. Mecanobiología de los huesos maxilares. II. Remodelación ósea. Av Odontoestomatol 2008:177-86.
10. Woitge HW, Seibel MJ. Risk assessment for osteoporosis. II. Biochemical markers of bone turnover: bone resorption indices. Clin Lab Med 2000;20:503-25.
11. Frost HM. The mechanostat. A proposed pathogenetic mechanism of osteoporoses and the bone mass effects of mechanical and nonmechanical agents. Bone Miner 1987;2:73-85.
12. Schoenau E. El sistema muscular es el impulsor del desarrollo esquelético. Ann Nestlé [Esp] 2006;64:55-62.
13. Cointry GR, Capozza RF, Negri AL, Roldán EJ, Ferretti JL. Biomechanical background for a noninvasive assessment of bone strength and muscle-bone interactions. J Musculoskelet Neuronal Interact 2004;4:1-11.
14. Pérez Cano R, Galán Galán F. Fármacos antirreabsortivos óseos. En: Tratado de Reumatología. Ed Arán ISBN: 84-86725-35-6. Tomo II. 1998;2411-23.
15. Fernández-Tresguerres I, Alobera Gracía MA, Canto

Table 3. Regulators of the expression of OPG, RANKL and RANK (adapted from Hofbauer[23])

	OPG	RANKL	RANK
Calcitriol	↑↓	↑	↑
Oestrogens	↑	↓ / —	
Testosterone	↑↓	—	
Glucocorticoids	↓	↑	
PTH	↓	↑	
IL1		↑	↑
IL4			↓ / —
IL7		↑	
IL-13	↑	↑	—
IL-17	↓	↑	—
TNF-α		↑	
Interferon γ	↑	↑	↑
PGE_2	↓	↑	
TGF-β	↑	↑↓	—
BMP_2	↑		—

↑ increase the expression; ↓ diminish the expression; — no changes were observed

Glossary

BMPs	Bone morphogenic proteins
M-CFU	Macrophage colony-forming units
M-CSF	Macrophage colony-stimulating factor
CTx	C-terminal telopeptide of type 1 collagen
FGF	Fibroblastic growth factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
IFN-γ	Interferon γ
IGF	Insulin-like growth factor
IL	Interleukin
MBR	Markers for bone remodelling
NO	Nitric oxide
NTx	TN-terminal telopeptide of type 1 collagen
OP	Osteoporosis
OPG	Osteoprotegerin
PDGF	Platelet derived growth factor
PGE	Prostaglandin E
PTH	Parathyroid hormone
RANK	Receptor activator for nuclear factor κβ
RANKL	Receptor activator for nuclear factor κβ ligand
TGF-β	Transforming growth factor
TNF-α	Tumour necrosis factor
BMU	Basic multicellular unit

Pingarrón M, Blanco Jerez L. Bases fisiológicas de la regeneración ósea II. El proceso de remodelado. Med oral patol oral cir bucal (Internet) [revista en Internet]. 2006 Abr;11(2):151-7 Citado 12.09.2009.Disponible en: http://scielo.isciii.es/scielo.php?script=sci_arttext&pid=S1698-69462006000200012&lng=es.
16. Harvey S, Hull KL. Growth hormone. A paracrine growth factor? Endocrine 1998;7:267-79.
17. Riggs BL, Spelsberg TC. Mechanisms of estrogen action on bone cells. In: Papapoulus SE, Lips P, Pols HAP, Johnston CC, Delmas PD (eds). Osteoporosis. New York Elsevier, 1996. p.241-50.
18. Fiter J, Nolla JM. Fisiopatología: remodelado óseo en el anciano. En: Osteoporosis. Guía de buena práctica clínica en Geriatría. Osteoporosis. 2004. Sociedad Española de Geriatría y gerontología. Ed. Mesa MP, Guañabens N. 21-34. Citado el 08.09.2009. Disponible en: http://www.scribd.com/doc/6696048/Gui-a-Osteoporosis.
19. Kanczler JM, Sahinoglu CR, Stevens CR, Blake DR. The complex influences of reactive oxygen species. In: Hukkanen M, Polak J, Hughes S. Nitric oxide in bone and joint disease. Cambridge University Press 1998.
20. Mundy GR, Boyce B, Hughes D, Wright K, Bonewald L, Dallas S, et al. The effects of cytokines and growth factors on osteoblastic cells. Bone 1995;17(Suppl.2):71S-5S.
21. Kostenuik PJ. Osteoprotegerin and RANKL regulate bone resorption, density, geometry and strength. Curr Opin Pharmacol 2005;5:618-25.
22. Kearns AE, Khosla S, Kostenuik PJ. Receptor activator of nuclear factor kappaB ligand and osteoprotegerin regulation of bone remodeling in health and disease. Endocr Rev 2008;29:155-92.
23. Boyce BF, Xing L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch Biochem Biophys 2008;473:139-46.
24. Vega D, Maalouf NM, Sakhaee K. The role of receptor activator of nuclear factor-kappaB (RANK)/RANK ligand/osteoprotegerin: clinical implications. J Clin Endocrinol Metab 2007;92:4514-21.
25. Geusens P. Emerging treatments for postmenopausal osteoporosis - focus on denosumab. Clin Interv Aging 2009;4:241-50.
26. Daroszewska A, Ralston SH. Mechanisms of disease: genetics of Paget's disease of bone and related disorders. Nat Clin Pract Rheumatol 2006;2:270-7.
27. Hofbauer LC, Schoppet M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA 2004;292:490-5.
28. Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, Saad F, et al; Denosumab HALT Prostate Cancer Study Group. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. N Engl J Med 2009;361:745-55.
29. Body JJ, Facon T, Coleman RE, Lipton A, Geurs F, Fan M, et al. A study of the biological receptor activator of nuclear factor-kappaB ligand inhibitor, denosumab, in patients with multiple myeloma or bone metastases from breast cancer. Clin Cancer Res 2006;12:1221-8.
30. Cohen SB, Dore RK, Lane NE, Ory PA, Peterfy CG, Sharp JT, et al. Denosumab Rheumatoid Arthritis Study Group. Denosumab treatment effects on structural damage, bone mineral density, and bone turnover in rheumatoid arthritis: a twelve-month, multicenter, randomized, double-blind, placebo-controlled, phase II clinical trial. Arthritis Rheum 2008;58:1299-309.
31. Sharp JT, Tsuji W, Ory P, Harper-Barek C, Wang H, Newmark R. Denosumab prevents metacarpal shaft cortical bone loss in patients with erosive rheumatoid arthritis. Arthritis Care Res (Hoboken) 2010;62:537-44.
32. Deodhar A, Dore RK, Mandel D, Schechtman J, Shergy W, Trapp R, et al. Denosumab-mediated increase in hand bone mineral density associated with decreased progression of bone erosion in rheumatoid arthritis patients. Arthritis Care Res (Hoboken) 2010;62:569-74.

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Fibromyalgia and osteoporosis

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Summary
Fibromyalgia (FM) is a syndrome characterised by the presence of diffuse chronic body pain which is associated with tenderness at certain sensitive points. Symptoms such as fatigue, altered sleep patterns or depression reduce the quality of life of these patients, reducing their physical activity. This may enhance the risk of osteoporosis. Various works have analysed the bone mass and levels of vitamin D in patients with FM, but the results are not conclusive.

Key words: *fibromyalgia, osteoporosis, vitamin D.*

Introduction
Fibromyalgia (FM) is a syndrome characterised by diffuse chronic pain associated with the presence of pain on the palpation of specific sensitive points located in certain parts of the body, in the absence of an organic disease which would justify it. It is frequently associated with other symptoms such as fatigue, headache, sleep disorders, and other functional disorders[1,2,3].

Historically, it was Sir William R Gowers[4] (1845-1915) who was the first to introduce the term "fibrositis" to describe the occurrence of muscular hypersensitivity in the regional pain syndromes, in which he thought he had found fibrous nodules made up of collagen tissue and nerve endings extremely painful to pressure and mechanical muscular force. During the second half of the 20th century there were notable advances in the clinical, pathogenic and conceptual aspects of the process. The modern history of the disease starts with Smythe[5] who, in 1972, systematised the "tender points" and established the first diagnostic criteria. In 1976, Hench[6] proposed, and used for the first time, the term FM to highlight the importance of these painful phenomena and the absence of inflammatory data, which on the other hand presupposed the term "fibrositis". In 1981, Yunus[7] reframed the current criteria to date, introducing additional aspects over and above the pain. In 1990 the American College of Rheumatology (ACR)[1] developed the classification criteria for FM. Over the past 20 years, a series of objections to these criteria have been developed, such as the difficulty in counting these tender points, which is carried out very seldomly and incorrectly, and the lack of consideration of the seriousness of the symptoms. With these new requirements, the ACR created in 2010 some preliminary diagnostic criteria for FM not based on tender points[8].

In FM, various circumstances occur which makes one think that osteoporosis (OP) may be more frequent in this condition than in the rest of the population. It is often associated with depression[9,10] and other personality changes[11,12], possibly due to a reduction in daily activity as a consequence of the pain, and as such, to a lower exposure to sun. A vitamin D deficit may be associated with the presence of musculoskeletal pain[13]. Low levels of physical activity[14] or depression in adult subjects[15] have been associated with low levels of vitamin D. Finally, some drugs used in the symptomatic treatment of FM may alter the bone[16].

The sum of these factors leads to the suspicion that patients with FM may have an increased risk of having OP. Various studies have been carried out which analyse bone mineral density (BMD) in patients with FM, but the results obtained have been uncertain. This is why we wished to carry out a review of the literature on this matter.

Levels of vitamin D in patients with fibromyalgia

Patients with FM are physically inactive, which results in a lower exposure to sun, and, therefore, a higher risk of hypovitaminosis D. A deficiency in vitamin D in these patients may increase musculoskeletal alterations, and the risk of falls.

Some works have shown a relationship between FM and low levels of vitamin D. Al-Allaf et al.[17] determined the levels of 25 hydroxyvitamin D (25-OHD) in 77 premenopausal women, of whom 40 had FM, with the other 37 being healthy. They found a high prevalence of hypovitaminosis D (defined as 25-OHD < 8 ng/ml) in the FM group (45%) compared with the control group (19%) (p< 0.015). Huisman et al.[18] analysed the levels of vitamin D metabolites (25-OHD and 1,25 OHD) in 25 women with FM and a similar number of women with Systemic lupus erythematosus (SLE), finding no differences; the prevalence of hypovitaminosis D (defined in this case as 25-OHD < 20 ng/ml) was high in both groups (48% FM, 58% SEL). According to the authors the use of drugs such as hydroychloroquine, which modifies the conversion of 25-OHD to 1,25-OHD, may explain the deficiency in SEL, but in FM it may be due to other factors such as lower exposure to sun or to dietary disorders.

A more recent work[19], carried out in 75 caucasian patients with FM (5 men and 70 women), found a high prevalence of hypovitaminosis D in this population. Specifically, 13% of the cases had 25-OHD < 10 ng/ml, 56% between 10-20 ng/ml and only 31% with levels of ≥ 20 ng/ml. Despite having made an assessment using the FIQ scale to measure the impact of FM on the quality of life (state of health and functional affectation in patients with FM), no relationship was found between the levels of vitamin D and the musculoskeletal symptoms.

We would now like to mention the works of other authors who have analysed the levels of vitamin D in patients with chronic pain, although not necessarily with FM. Plotnikoff et al.[20] determined the prevalence of hypovitaminosis D in 150 patients of both sexes and of 6 ethnic groups, who suffered non-specific persistent (> 2 months) musculoskeletal pain and which did not respond well to standard treatment. 93% of the total of these patients had low levels of vitamin D (25-OHD < 20 ng/ml), specifically, 83% of the white patients, 89% of the Asians, and 100% of the African-Americans, Native Americans and Hispanic patients. There were no differences by sex. Block et al.[21], cognisant of this study, determined the levels of vitamin D in 101 white patients of both sexes who suffered generalised non-specific chronic musculoskeletal pain. Two thirds of these patients (69) met the ARC criteria for FM and the remaining third formed the control group. The average level of vitamin D was similar in both groups, although the prevalence of hypovitaminosis D (25-OHD < 20 ng/ml) was higher in the FM group than in the control group (48% vs 28%). Levels lower than 10 ng/ml were detected in 12% of the patients with FM, as against 3% in the control group. In 2008, Mouyis et al.[22] compared the levels of 25-OHD in patients diagnosed with OP/osteopenia (n= 122) with a group of rheumatology patients followed up in an outpatients clinic (n= 141), observing that the levels of 25-OHD were significantly lower in the rheumatology patients. Specifically, those subgroups with inflammatory arthritis and chronic pain/FM had lower levels. More recently, McBeth et al.[13] analysed levels in 3,075 people (8.6% with chronic diffuse pain, 50.4% with "other pain" which did not satisfy the criteria for diffuse chronic pain, and 41% controls) observing that, after adjusting for age and physical activity those patients with "other pain" and with chronic diffuse pain had lower levels of 25-OHD than the control group. A study carried out in the British population by Atherton et al.[23] in 2009, in people of both sexes, found an inverse relationship between levels of vitamin D (25-OHD) and the suffering of chronic diffuse pain, but only in women. However, this relationship disappeared after adjusting for confusion factors. Tandeter et al.[24] analysed the possible relationship between low levels of vitamin D and non-specific musculoskeletal pain (including patients with FM) in premenopausal women. They analysed this relationship in 68 women with FM and 82 without, not finding a relationship in either. Neither did Warner et al.[25], comparing 184 patients with diffuse pain and 104 with osteoarthritis (taken as the control group) find a difference in 25-OHD between the two groups (29.2 ng/mL vs 28.8 ng/mL; p= 0.78). Nor were there differences in the percentages of patients with levels of 25-OHD ≤ 20 ng/mL (29% in patients with diffuse pain and 20% in those with osteoarthritis; p= 0,09). These authors administered vitamin D supplements, as opposed to a placebo, in 50 of their patients with diffuse pain and levels of 25-OHD ≤ 20 mL, over 3 months, confirming that the treatment with vitamin D did not have any effect on the pain in comparison with the placebo. In accord with these works, Ulusoy et al.[26] compared, in 2010, the levels of 25-OHD in 30 women with FM compared with 30 healthy women of the same age, without finding any differences. Neither did Rzende et al.[27] find any such differences in a transverse study which compared levels of 25-OHD in 87 patients with FM with a control group made up of participants without chronic musculoskeletal pain. The majority of these works failed to conclude that the prevalence of hypovitaminosis D was higher in patients with FM, although the studies are quite heterogeneous.

Fibromyalgia and osteoporosis

FM and OP share risk factors in common, and some medicines which alleviate the symptoms of FM may alter bone metabolism. Thus it has been suggested that the incidence of OP may be increased in those patients with FM.

1. Sex

Both OP and of FM are predominant in women. A study carried out by Yunus[28] to evaluate the role of sex in FM indicated a 9:1 proportion in favour of women. It is also calculated that OP is 3 times more frequent in women than in men.

2. Age

Both the prevalence of OP, and that of FM, increase with age. In the study of Wolfe[29] FM reached its maximum prevalence between the ages of 60 and 79 years. A later study by White[30] confirmed that the symptoms of FM intensify with age. Age is also a clear risk factor for the development of osteoporosis[31].

3. Hygiene-dietary habits and lifestyle factors

Smoking exacerbates the pain symptoms in patients with FM[32] and its deleterious effects on bone are well known.

It has been demonstrated repeatedly that physical exercise has a beneficial role in the attainment of peak bone mass[33,34], and that it is associated with an increase in bone mineral density (BMD)[35]. Physical inactivity is common in women with FM, often the consequence of pain, which constitutes another risk factor for the development of osteoporosis[36].

Dietary disorders may influence the development of osteoporosis. In FM, a higher prevalence of irritable bowel syndrome has been described[37], which is frequently associated with lactose intolerance, which can cause BMD loss in these patients.

Patients with FM have a higher risk of anxiety-depressive disorders[38]. The association between depression and changes in bone mass has been well documented[39]. Depression may take place in a weakened state, with protein deficiency, a decrease in calcium and vitamin supply and a reduction in levels of IGF-1[40]. In addition, depression is associated with other risk factors for osteoporosis, such as physical inactivity due to fatigue, pain, quality of sleep and symptoms of depression.

4. Hormonal factors

In FM, there are neuroendocrine alterations which may favour the development of osteoporosis.

A) Sex hormones:

A study[41] has evaluated the reproductive history of women between 35 and 74 years of age with FM (n= 36, with chronic diffuse pain without FM (n= 44), and without chronic pain (n= 408), finding that the women with FM had a later menarche (OR= 2.2 for > 14 years). Another work[42] has determined the levels of adrenal androgens and its metabolites in 57 women with FM and 114 healthy controls. The levels of dehydroepiandrosterone (DHEA) were lower in the premenopausal (2.4 vs 4.8 µmol/l; p< 0.0001) and postmenopausal patients (1.2 vs 2.4 µmol/l; p< 0.001) with FM compared with their controls. Levels of testosterone were lower in premenopausal women with FM, but not in the postmenopausal women (2.36 vs 4.93 pmol/l; p< 0.0001). These results suggest adrenocortical hypofunction of the sex steroid metabolism, which could have an influence on the bone.

B) IGF-1:

The insulin-like growth factor type 1 (IGF-1) stimulates bone formation, exerting an anabolic influence on the bone[43]. Its deficiency has been related to the development of OP[44]. Some studies indicate that blood levels of IGF-1 are reduced in FM[45,46,47]. This may constitute a risk factor for the development of low bone mass. Bennett et al.[48] have shown that in 500 women with FM, as against 126 healthy women, levels of IGF-1 are lower in the patients (138 ± 56 ng/ml vs 215 ± 86 ng/ml; p< 0.001), whilst a more recent study[49] describes levels of IGF-1 26% lower in women with FM compared with healthy women.

5. Use of medication

Certain drugs used in the treatment of FM may alter bone metabolism.

The anti-depressive selective serotonin reuptake inhibitors reduce the symptoms of FM[50]. It has been reported that these drugs may reduce BMD. In addition, they increase the risk of amenorrhea[51]. The benzodiazepines, well used in FM, are associated with a higher risk of falls and bone fractures[52,53]. The anti-epileptics, used in the treatment of neuropathic pain,[54,55] may cause hypovitaminosis D and osteomalacia.

Studies of bone mass in patients with fibromyalgia

The first authors who studied the alterations in bone metabolism in patients with FM were Appelboom et al.[56], in 1990 analysing the BMD, using DXA in the lumbar spine (LS) and hip, of 44 premenopausal women of 26-50 years of age (28 with FM and 16 controls with other soft tissue rheumatisms). No differences were found in bone mass between the two groups in any location, after adjusting for the degree of physical activity and diseases or treatments which could modify bone metabolism. However, they did report an increase in bone remodelling in patients with FM, determined using radioisotopes (pyrophosphate bonded with technetium [Tc-PPi]) with a higher retention of Tc-PPi.

In a later (posterior) study[57], the BMD in LS measured by DXA was analysed in 24 women with FM and 48 healthy women (30-60 years of age). Stratifying the women by decades of age (31-40, 41-50, 51-60) they found that the women with FM had, at all ages, a lower bone mass in the LS (T-score = -0.31 vs -0.16 between 31- and 40 years,

-0.19 vs 0.04 between 41 and 50 years and -1.40 vs -0.25 between 51 and 60 years). In the femoral neck (FN) however, they only found differences in the decade 51-60 years (T-score = -1.97 vs -0.9; p< 0.005).

Another work[58] studied, using ultrasound (US) of the calcaneum, 116 women with FM and 141 control women, all of whom were premenopausal. It found no differences between the two groups, but the control women were slightly taller and with a lower body mass index (BMI); after correcting for weight, the results were lower in the FM group. In the same vein, another work[17] analysed the BMD with US (calcaneum) and DXA (LS and distal forearm) in 40 premenopausal women with FM and 37 healthy women of the same age, and found no difference either by US or by DXA (BMD in LS, 1.248 g/cm^2 in FM vs 1.240 g/cm^2 in the controls), However, the BMD in the distal third of the forearm was lower in patients with FM (0.699 g/cm^2 vs 0.724 g/cm^2; p= 0.02).

Other authors have evaluated the influence of risk factors, such as depression or physical activity, on the development of osteoporosis in these patients. Erdal et al.[59] evaluated the BMD through DXA in the LS and FN in 38 women with FM and 20 healthy controls (25-50 years), determining also their level of depression with the Beck scale. The BMD was lower in the FM group with respect to the control group, both in the LS (DMO= 0.950 ± 9.902 vs 1.000 ± 6.082; p= 0.026) and in the FN (DMO 0.840 ± 0.123 vs 0.920 ± 7.654; p= 0.003), finding a negative correlation between Beck's scale of depression and values of BMD in both locations (r= -0.53, p= 0.001 in LS; r= -0.47, p= 0.003 in FN) in all the women combined. Jensen et al.[60] analysed BMD (using DXA in the LS and FN) in 31 women with FM (20 premenopausal and 11 postmenopausal) and 40 healthy women (30 premenopausal and 10 postmenopausal), applying, also, the VAS scale for pain and studying the degree of physical activity in daily life with FIQ. They found no differences in BMD in either of the two locations, although in the premenopausal women with FM the BMD in LS was correlated negatively with the degree of pain and the FIQ score (r= -0.52; p= 0.003; and r= -0.31; p= 0.9, respectively, from which the authors conclude that the severity of FM can have a negative impact on bone mass.

Another, older, work, and with a lower number of patients[61], studied in 24 premenopausal women (12 with FM and 12 healthy) the BMD using DPA (dual photon absorptiometry) in LS and FN, as well as makers for bone remodelling in the blood (alkaline phosphatase and osteocalcin) and urine (calcium/creatinine and hydroxyproline). They found no differences either in bone mass or in markers for bone formation between the two groups, but they did observe that the calcium/creatinine quotients in urine were higher in the women with FM than in the control group (0.35 vs 0.19 mM/mM [p= 0.01] y 22 vs 12 µM/mM [p= 0.002], respectively), which appears to indicate an increase in bone resorption in these women. More recent studies have also failed to clarify the possible association between low BMD and FM. Ulusoy et al.[26] found no differences in BMD in either the lumbar spine or the femoral neck, after an analysis of 30 women with FM and 30 healthy controls of the same age.

Other works have analysed markers for bone remodelling in patients with FM. Maghraoui et al.[62] measured blood levels of osteocalcin, crosslaps (CTX) and parathyroid hormone (PTH) in 81 people (41 healthy, 40 with FM), finding that those patients with FM had blood levels of CTX and PTH lower than the control group, from which the authors conclude that the patients with FM had reduced bone resorption.

Conclusion

FM is a disease characterised by the presence of diffuse chronic pain, associated with other symptoms such as fatigue, depression or non-restorative sleep. This disease has risk factors in common with osteoporosis. Various works have analysed bone mass and levels of vitamin D in patients with FM, but the results are less than conclusive. In addition, most of these studies have been carried out with a low number of patients and with highly heterogeneous control groups. New works are needed which will analyse in depth the association between these two diseases.

Bibliography

1. Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the multicenter criteria committee. Arthritis Rheum 1990;33:160-72.
2. Ballina García FJ, Martín Lascuevas P, Iglesias García A, Hernández Mejía R, Cueto Espinar A. La fibromialgia. Revisión Clínica. Rev Clin Esp 1995;195:54-61.
3. Mease P, Arnold LM, Bennett R, Boonen A, Buskila D, Carville S, et al. Fibromyalgia syndrome. Rheumatol 2007;34:1415-25.
4. Gowers WR. A lecture on lumbago. Its lessons and analogues. Br Med J 1904;1:117-21.
5 Smythe HA, Moldofsky H. Two contributions to understanding of the "fibrositis" syndrome. Bull Rheum Dis 1977;28:928-31.
6. Hench PK. Nonarticular Rheumatism. 22nd rheumatism review: review of the American and English literature for the years 1973 and 1974. Arthritis Rheum 1976;19:1081-9.
7. Yunus MB, Masi AT, Calabro JJ, Miller KA, Feigenbaum SL. Primary fibromyalgia (fibrositis): clinical study of 50 patients with matched controls. Semin Arthritis Rheum 1981;11:151-71.
8. Wolfe F, Clauw DJ, Fitzcharles MA, Goldenberg DL, Katz RS, Maise P, et al. The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. Arthritis Care Res 2010;62:600-10.
9. Weir PT, Harlan GA, Nkoy FL, Jones SS, Hegmann KT, Gren LH, et al. The incidence of fibromyalgia and its associated comorbidities: a population-based retrospective cohort study based on International Classification of Diseases, 9th Revision codes. J Clin Rheumatol 2006;12:124-8.
10. Patten SB, Beck CA, Kassam A, Williams JV, Barbui C,

Metz LM. Long-term medical conditions and major depression: strength os association for specific conditions in the general population. Can J Psychiatry 2005;50:195-202.
11. Besteiro J, Álvarez M, Lemos S, Muñiz J, Costas C, Weruaga A. Dimensiones de personalidad, sentido de coherencia y salud percibida en pacientes con un síndrome fibromiálgico. Int J Clin Health Psychol 2008;8:411-27.
12. Arnold LM, Hudson JI, Keck PE Jr., Auchenbach MB, Javaras KN, Hess EV. Comorbidity of fibromyalgia and psychiatric disorders. J Clin Psychiatry 2006;67:1219-25.
13. McBeth J, Pye SR, O'Neill TW, Macfarlane GJ, Tajar A, Bartfai G, et al. EMAS Group. Musculoskeletal pain is associated with very low levels of vitamin D in men: results from the European Male Ageing Study. Ann Rheum Dis 2010;69:1448-52.
14. Scragg R, Camargo CA Jr. Frecuency of leisure-time physical actitity and serum 25-hydroxyvitamin D levels in the US population: results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol 2008;168:577-86.
15. Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, Penninx BW. Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. Arch Gen Psychiatry 2008;65:508-12.
16. Mazziotti G, Canalis E, Giustina A. Drug-induced osteoporosis: mechanisms and clinical implications. Am J Med 2010;123:877-84.
17. Al-Allaf AW, Mole PA, Paterson CR, Pullar T. Bone health in patiens with fibromyalgia. Rheumatology 2003;42:1202-6.
18. Huisman AM, White KP, Algra A, Harth M, Vieth R, Jacobs JW, et al. Vitamin D levels in women with systemic lupus erythematosus and fibromialgia. J Rheumatol 2001;28:2535-9.
19. Armstrong DJ, Meenagh GK, Bickle I, Lee AS, Curran ES, Finch MB. Vitamin D deficiency is associated with anxiety and depression in fibromialgia. Clin Rheumatol 2007;26:551-4.
20. Plotnikoff GA, Quigley J. Prevalence of severe hypovitaminosis D in patients with persistent, nonspecific musculoskeletal pain. Mayo Clin Proc 2003;78:1463-70.
21. Block SR. Vitamin D deficiency is not associated with non-specific musculoskeletal pain syndromes including fibromyalgia. Mayo Clin Proc 2004;79:1585-6.
22. Mouyis M, Ostor AJK, Crisp AJ, Ginawi A, Halsall DJ, Shenker N, Poole KES. Hypovitaminosis D among rheumatology outpatients in clinical practice. Rheumatology 2008;47:1348-51.
23. Atherton K, Berry DJ, Parsons T, Macfarlane GJ, Power C, Hypponen E. Vitamin D and chronic widespread pain in a white middle-aged British population: evidence from a cross-sectional population survey. Ann Rheum Dis 2009;68:817-22.
24. Tandeter H, Grynbaum M, Zuili I, Shany S, Shvartzman P. Serum 25-OH vitamin D levels in patients with fibromyalgia. Isr Med Assoc J 2009;11:339-42.
25. Warner AE, Arnspiger SA. Diffuse musculoskeletal pain is not associated with low vitamin D levels or improved by treatment with vitamin D. J Clin Rheumatol 2008;14:12-6.
26. Ulusoy H, Sarica N, Arslan S, Ozyurt H, Cetin I, Birgul Ozer E, et al. Serum vitamin D status and bone mineral density in fibromyalgia. Bratisl Lek Listy 2010;111:604-9.
27. de Rezende Pena C, Grillo LP; das Chagas Medeiros MM. Evaluation of 25-hydroxyvitamin D serum levels in patients with fibromyalgia. J Clin Rheumatol 2010;16:365-9.
28. Yunus MB. The role of gender in fibromyalgia syndrome. Curr Rheumatol Rep 2001;3:128-34.
29. Wolfe F, Ross K, Anderson J, Russell IJ, Herbert L. The prevalence and characteristics of fibromyalgia in the general population. Arthritis Rheum 1995;38:19-28.
30. White KP, Speechley M, Harth M, Ostbye T. The London Fibromyalgia Epidemiology Study: Comparing the demographic and clinical characteristics in 100 random community cases of fibromialgia versus controls. J Rheumatol 1999;26:1577-85.
31. Riancho Moral JA, González Macías J. Osteoporosis: Definición y etiología. Riancho Moral JA, González Macías J. (eds.) Manual práctico de Osteoporosis y Enfermedades del Metabolismo Mineral. Madrid: Jarpyo; 2004. pp. 99-104.
32. Yunus MB, Arslan S, Aldag JC. Relationship between fibromialgia features and smoking. Scand J Rheumatol 2002;31:301-5.
33. Sowers MF. Lower peak bone mass and its decline. Baillieres Best Pract Res Clin Endocrinol Metab 2000;14:317-29.
34. Black DM, Cooper C. Epidemiology of fractures and assessment of fracture risk. Clin Lab Med 2000;20:439-53.
35. Berard A, Bravo G, Gauthier P. Meta-analysis of the effectiveness of physical activity for the prevention of bone loss in postmenopausal women. Osteoporos Int 1997;7:331-7.
36. Espallargues M, Sampietro-Colom L, Estrada MD, Solà M, del Rio L, Setoain J, et al. Identifying bone-mass-related risk factors for fracture to guide bone densitometry measurements: a systematic review of the literature. Osteoporos Int 2001;12:811-22.
37. Yunus MB, Masi AT, Aldag JC. A controlled study of primary fibromyalgia syndrome: Clinical features and association with other functional syndromes. J Rheumatol Suppl 1989;19:62-71.
38. Hudson JI, Hudson MS, Pliner LF, Goldenberg DL, Pope HG Jr. Fibromyalgia and major affective disorder: a controlled phenomenology and family history study. Am J Psychiatry 1985;142:441-6.
39. Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, Chrousos G, et al. Bone mineral density in women with depression. N Engl J Med 1996;335:1176-81.
40. Bonjour JP, Schurch MA, Chevalley T, Ammann P, Rizzoli R. Protein intake, IGF-1 and osteoporosis. Osteoporosis Int 1997;7:836-42.
41. Schochat T, Beckmann C. Sociodemographic characteristics, risk factors and reproductive history in subjects with fibromialgia. Results of a population-based case-control study. Z Rheumatol 2003;62:46-59.
42. Dessein PH, Shipton EA, Goffe BI, Hadebe DP, Stanwix AE, Van der Merwe BA. Hyposecretion of adrenal androgens and the relation of serum adrenal steroids, serotonin, insulin-like growth factor I to clinical features in women with fibromialgia. Pain 1999;82:313-9.
43. Riancho JA, Gónzalez Macías J. Otras hormonas: hormonas tiroideas, GH, glucocorticoides. En: Riancho Moral JA, González Macías J. (eds.) Manual práctico de Osteoporosis y Enfermedades del Metabolismo Mineral. Madrid: Jarpyo; 2004. pp.45-8.
44. Giustina A, Mazziotti G, Canalis E. Growth hormone, insuline-like growth factors and the skeleton. Endocr Rev 2008:29;535-59.
45. Landis CA, Lentz MJ, Rothermel J, Riffle SC, Chapman D, and Buchwald D, et al. Decreased nocturnal levels of prolactin and growth hormone in women with fibromyalgia. J Clin Endocrinol Metab 2001;86:1672-8.
46. Bagge E, Bengtsson BA, Carlsson L, Carlsson J. Low growth hormone secretion in patients with fibromyalgia - a preliminary report on 10 patients and 10 controls. J Rheumatol 1998;25:145-8.
47. Bennett RM. Adult growth hormone deficiency in patients with fibromialgia. Curr Rheumatol Rep 2002;4:306-12.
48. Bennett RM, Cook DM, Clark SR, Burckhardt CS, Campbell SM. Hypothalamic-Pituitary-Insulin-like growth factor-I axis dysfunction in patients with fibromialgia. J Rheumatol 1997;24:1384-9.
49. Armagan O, Sirmagul E, Sirmagul B. The levels of IGF-1 and their relationship with bone mineral density in the premenopausal women with fibromyalgia síndrome. Rheumatism 2008;23:118-23.

50. Miller LJ, Kubes KL. Serotoninergic agents in the trearment of fibromyalgia syndrome. Ann Pharmacother 2002;36:707-12.
51. Goodnick PJ, Claudry T, Artady J, Arcey S. Women´s issues in mood disorders. Expert Opin Pharmacother 2000;1:903-16.
52. Vestergaard P. Skeletal effects of central nervous system active drugs: anxiolytics, sedatives, antidepressants, lithium and neuroleptics. Curr Drug Saf 2008;3:185-9.
53. Vestergaard P, Rejnmark L, Mosekilde L. Anxiolytics, sedatives, antidepressants, neuroleptics and the risk of fracture. Osteoporos Int 2006;17:807-16.
54. Tremont-Lukats IW, Megeff C, Backomja MM. Anticonvulsants for neuropathic pain syndromes: mechanisms of action and place in therapy. Drugs 2000;60:1029-52.
55. Rice AS, Maton S. Gabapentin in postherpetic neuralgia: a randomised, double blind, placebo controlled study. Pain 2001;94:215-24.
56. Appelboom T, Schoutens A. High bone turnover in fibromyalgia. Calcif Tissue Int 1990;46:314-7.
57. Swezey RL, Adams J. Fibromyalgia: A risk factor for osteoporosis. J Rheumatology 1999;26:2642-4.
58. Zerahn B, Bliddal H, Moller P, Burgwardt A, Danneskiold-Samsoe B. Bone mass in the calcaneus in patients with fibromyalgia. J Musculoskeletal Pain 2001;9:17-23.
59. Erdal A, Yildirim K, Hacibeyoglu H. The bone mineral density values in fibromyalgia síndrome. Osteoporoz Dünyasindan 2003;9:59-62.
60. Jensen B, Wittrup IH, Bliddal H, Danneskiold-Samsøe B, Faber J. Bone mineral density in fibromialgia patients-correlation to disease activity. Scand J Rheumatol 2003;32:146-50.
61. Jacobsen S, Gam A, Egsmose C, Olsen M, Danneskiold-Samsoe B, Jensen GF. Bone mass and turnover in fibromyalgia. J Rheumatol 1993;20:856-9.
62. El Maghraoui A, Tellal S, Achemlal L, Nouijai A, Ghazi M, Mounach A, et al. Bone turnover and hormonal perturbations in patients with fibromyalgia. Clin Exp Rheumatol 2006;24:428-31.

Evolution of bone mineral density after a 15 year intervention based on progressive force training

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Dear Editor,

Osteoporosis is the most common bone disorder in humans, affecting older people at a very high rate. It consists of an imbalance in bone formation-resorption which principally affects its strength and resistance, resulting in an increase in risk of fractures[1]. This situation is associated with high levels of morbidity and mortality[2]. One of the many causes which affect this relationship is the history of the mechanical load taken by the bone[3], and, according to the law proposed by Dr Wolff, the stress or mechanical load applied to the bone through the tendon and generated by the muscle. Pharmacological intervention for osteoporosis includes drugs of the biphosphonate family, the selective oestrogen receptor modulators, parathyroid hormone, the oestrogens and calcitonin[2]. In addition, the referent institutions and the specialists agree in including the practice of physical exercise among health-giving habits for people affected, or with possible affectation of bone mineralisation[2]. However, there is a need to evaluate longitudinal studies of physical exercise[3], given that bone improvements happen 4-6 months after the start of intervention, but only after a year will these changes become significant[3]. Similarly, Beck et al.[4] have found that, despite the abundant scientific evidence which relates resistance exercise with oestrogen stimulus, the changes in bone mineral density are usually modest. Therefore, it seems logical to think about the necessity of carrying out long term longitudinal studies to be able to observe changes resulting from the application of a resistance exercise programme.

Table 1. Percentage change in initial values and final values after the intervention. The percentage change has been calculated using the formula:

% change = [(post-pre)/pre]x100

	1995	2009	% change
Femoral neck	640 g/cm²	866 g/cm²	35.31%
L2-L4	729 g/cm²	994 g/cm²	36.35%

Thus we have evaluated an intervention using a progressive force training programme over 15 years in a 64 year old woman who was receiving standard antiresorptive drug treatment (alendronate). The trial started in 1995, after finding out the degree of osteoporosis suffered by the subject of the study by measuring her bone mineral density with dual energy X-ray absorptiometry (DXA), both in the femoral neck and in the lumbar region. The annual check was carried out in the same clinic using the same machine. The training programme consisted of a programme of progressive neuromuscular conditioning based on the perfor-

mance of resistance exercises. Before starting the programme measurements were taken of maximum strength to enable the prescribing of exercise on the basis of the maximum voluntary load. Subsequently, 8 exercises were selected which involved all, the major muscle groups. The training programme was characterised by the performance of a series of warm-ups carried out with between 15 and 20 repetitions. After one minute of recuperation. 3 series were carried out, with 8-12 repetitions. This programme increase in frequency from one session a week during the first 6 years to two training sessions for the remaining 8 years. The other variable which experienced variation with the aim of contributing to the progression of the training was the load.

Our results (Table 1) show an annual progressive increase in bone mineral density of 2%. Assuming the potential limitations of carrying out the observation in a single case, in addition to receiving drug treatment, these data agree with those published my Suominen[5]. Their records determine that in people of advanced age the rhythm of annual progression of bone mineral density caused by the resistance exercise treatment may be between 1 and 3%[5]. The bibliographical search has found few studies whose period of intervention is similar to this case. However, our data are in line with earlier research which established the suitability of resistance exercise treatment as an efficacious measure, and as a tool synergistic with drug treatment for the treatment of osteoporosis. Finally, we note that over the period of treatment not a single fall or fracture was recorded.

Bibliography

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001;85:785-95.
2. Bonnick SL, Harris ST, Kendler DL, McClung MR, Silverman SL, and Board of Trustees of The North American Menopause Society (NAMS). Management of osteoporosis in postmenopausal women: 2010 position statement of The North American Menopause Society. Menopause 2010;17:25-54.
3. Guadalupe-Grau A, Fuentes T, Guerra B, Calbet JA. Exercise and bone mass in adults. Sports Med 2009;39:439-68.
4. Beck TJ, Kohlmeier LA, Petit MA, Wu G, Leboff MS, Cauley JA, et al. Confounders in the association between exercise and femur bone in postmenopausal women. Med Sci Sports Exerc 2011;43:80-9.
5. Suominen H. Muscle training for bone strength. Aging Clin Exp Res 2006;18:85-93.

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