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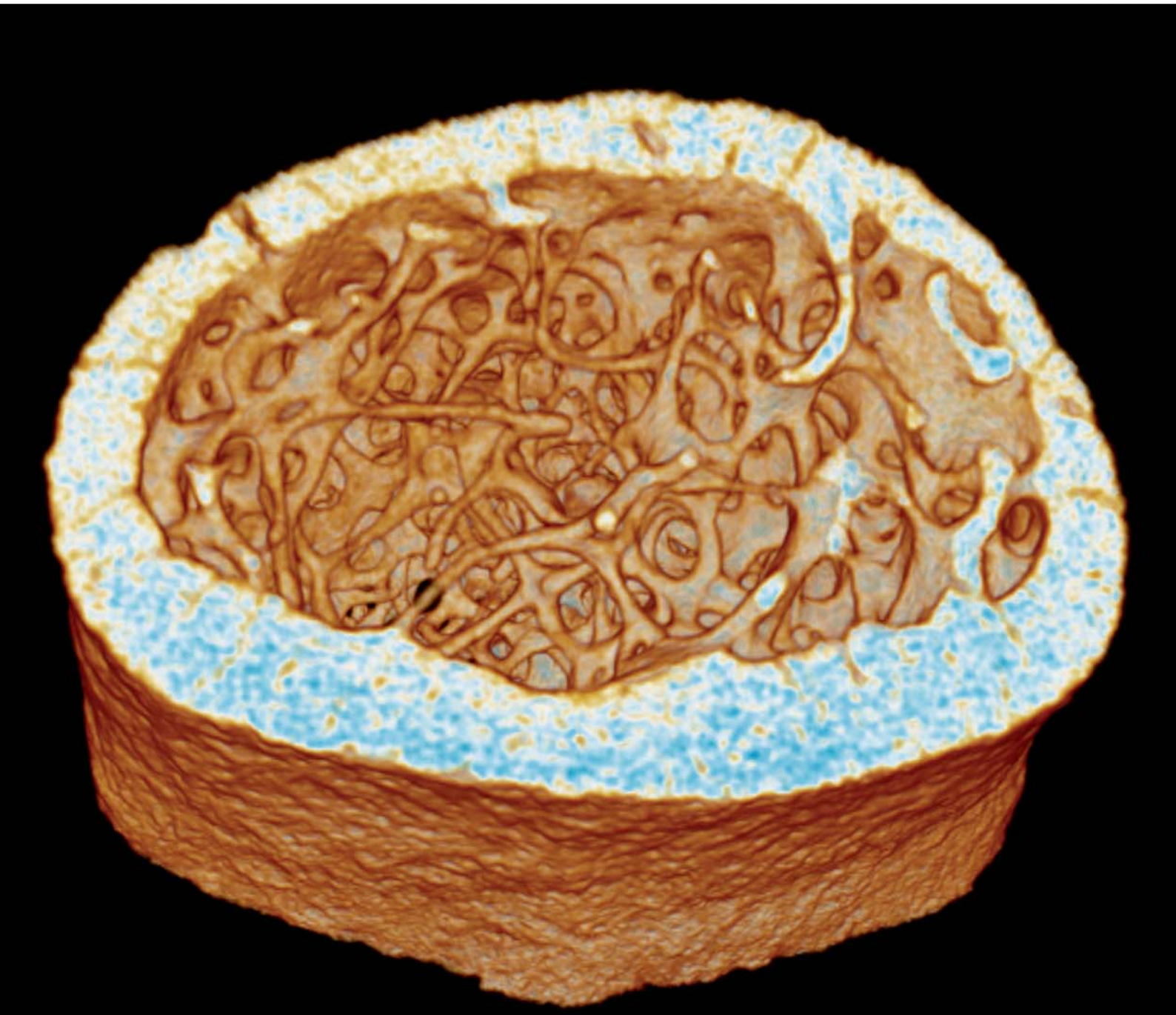

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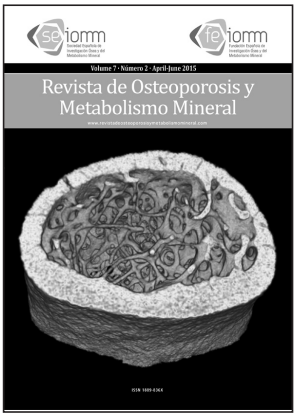

Our cover
Submetafisaria rat femur region studied by microTAC

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SUMMARY

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Hip fracture: an opportunity to treat osteoporosis?

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Fracture of the hip is the most serious complication of osteoporosis, not only due to the morbimortality it entails but due to the social-health costs which it generates[1]. However, in spite of this enormous impact, in practice the identification and treatment of osteoporosis and the adequate monitoring of those who have suffered a hip fracture is highly irregular[2].

In Spain, the use of antiosteoporotic medication is, in general and in the primary care setting in particular, higher in the group of women with an average age of 65 years. However, it is much lower in those at ages with a greater propensity to hip fracture[3,4]. Furthermore, in spite of the fact that the therapeutic arsenal for osteoporosis has increased notably in the last decade, the use of antiresorptive or osteoforming drugs after a hip fracture occurs is low, and has even reduced in countries such as the US[5].

The reasons for this low use of antiosteoporotic treatment in patients with fragility fractures are complex and probably different in different health systems. Nevertheless, it should be said, firstly, that the understanding of osteoporosis, and the risk of fracture and of its complications on the part of the population and the people who look after these patients, is not always adequate[6]. Secondly, the secondary effects associated with the use of antiresorptive drugs (osteonecrosis of the jaw, atypical femoral fractures, auricular fibrillation…) have played a role in recent years in the decision to initiate an antiosteoporotic treatment[7]. Lastly, one of the most significant reasons is the fragmentation in the care of these patients in different clinical settings (emergency services, traumatology and orthopaedic surgery, rheumatology, internal medicine, geriatrics, rehabilitation, primary care). In fact, in the last few years, the development of multidisciplinary fracture units have been promoted by the different medical societies. In line with this, a recent work, carried out in the United States, has demonstrated that this type of unit would be cost-effective and would result in a reduction in new fractures in those subjects presenting a hip fracture[8].

In this number of the Review of Osteoporosis and Mineral Metabolism, León Vásquez et al.,[9] analyse the variation in antiosteoporotic treatment before and after the occurrence of a hip fracture through the review of the database for pharmaco-epidemiological research in primary care (BIFAP), in the years from 2005 to 2010. However, with the limitations in the clinical records and those mentioned by the authors, they observed that around a quarter of the subjects who had suffered a fragility fracture of the hip received some anti-osteoporotic drug in the year before the fracture (in fact only 15% had had a diagnosis of osteoporosis recorded). Approximately half of the medicines prescribed were bisphosphonates, followed by calcitonin (12%), with the use of teriparatide being around 2% (no patient was recorded as having been treated with denosumab, given that is was not yet commercialised). As a whole, it represents a striking figure, which could be even lower, given that a patient is only considered to have been treated if they had completed at least two prescriptions of one of these agents or a single prescription if it had been completed in the last 6 months. It was also not possible to obtain information regarding the dose or the period of exposure to the drug. Furthermore, neither the persistence or adherence to treatment were analysed.

In the case of prescription of antiosteoporotic treatment after hip fracture, there was only evidence of a small increase (39% of patients). A third of the patients with fractures were receiving calcium and/or vitamin D supplements, while, overall, the prescription of an antiresorptive drug with efficacy in the hip (bisphosphonates and strontium ranelate) was around 25% (mainly alendronate and risedronate, in 20% of cases). The prescription of teriparatide after fracture was very low, (2%). The strongest predictor associated with the receipt of antiosteoporotic treatment after fracture was that the patient was female (OR: 2.4), followed by having had an earlier diagnosis of osteoporosis (OR: 1.61). It is worth noting that in this study all drugs prescribed within a year after the fracture were considered, without specifying the moment

at which their consumption was initiated, or the persistence or adherence to the treatments scheduled. Given that the study dealt with records in a primary care setting there were also no data regarding the prescription of zoledronic acid.

So, even with these limitations, these data from the BIFAP record, among others, do nothing but confirm the low use of antiosteoporotic drugs after a fragility fracture, and specifically, a fracture of the hip. Hence, the clinical records of patients with osteoporosis, such as the OSTEOMED register of the working group on osteoporosis of the Spanish Society of Internal Medicine, may be useful tools for identifying areas of improvement in the management of this disease and its complications.

In accordance with the above, the scientific and clinical societies involved must join forces to identify, adequately assess and closely monitor those patients with osteoporosis and fragility fractures with the aim of reducing the patients' risk of new fractures and improving their quality of life, while contributing to more efficient health systems. The formation of multidisciplinary clinical fracture units may contribute to the improvement in the approach to these patients, especially in ensuring adequate treatment of osteoporosis after a hip fracture.

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Use of bisphosphonates in postmenopausal women with rheumatoid arthritis; results of a multicentre study

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Summary

Objective: The objective of this study was to analyse the use of bisphosphonates in women with rheumatoid arthritis (RA) in the Canary Islands.

Material and methods: This multicentre observational study included women aged 50 years or over. At a single visit, demographic variables and those relating to the RA, history of fragility fractures, use of corticoids, performance of bone densitometry (DXA) and current treatment with bisphosphonates were recorded. The simplified FRAX ® tool was used and the recommendations of the American College of Rheumatology (ACR) for the prophylaxis of osteoporosis with corticoids were applied.

Results: 192 women were included, with an average age of 62 years. A total of 91 (48%) patients were receiving corticoids; 17 of these (9%) had suffered a fracture; 123 (66%) had had a DXA; and 52 (28%) were taking bisphosphonates (70% of the patients with osteoporosis or fracture and 45% of those with criteria for prophylactic use of corticoids for osteoporosis). Those factors having a significant association with the use of bisphosphonates were age, duration of the disease, the HAQ functional capacity questionnaire, the risk of fracture determined by FRAX®, treatment with corticoids, history of fracture and the previous performance of DXA. In the multivariate study only the DXA (p=0.03) and history of fracture (p=0.02) were significantly associated.

Conclusions: In postmenopausal women from the Canary Islands with RA the prescription of bisphosphonates could conform better to the guidelines, especially in patients receiving treatment with corticoids.

Key words: *rheumatoid arthritis, osteoporosis, fracture, bisphosphonates, bone densitometry.*

Introduction

Patients with rheumatoid arthritis (RA) have an increased risk of osteoporosis (OP) and of fracture. The prevalence of osteoporosis in RA is between 17% and 32% in the spine and between 15% and 36% in the hip[1,2]. In addition to the classic risk factors, the disease itself and the use of corticoids are considered as independent factors for the risk of fracture, as is outlined in the FRAX® tool[3]. In the clinical monitoring of the patient with RA, the rheumatologist takes into account the guides to the management of OP[4,5], as well as the guides to the prevention of corticoid-induced osteoporosis[6,7].

This study analyses the use of bisphosphonates in postmenopausal women with RA in clinical practice.

Material and methods

A multicentre observational study was carried out in five hospitals in the Canary Islands (four university hospitals and one district hospital), which included consecutive patients attending the rheumatology clinic. The study was approved by the ethics committee for clinical research of the University of Gran Canaria Dr Negrin Hospital, and the patients gave their written consent. The inclusion criteria were: women of 50 or more years of age attending a clinic with a diagnosis of RA (1997 and/or 2010 criteria). The exclusion criterion was that the arthritis had been developing for less than 6 months.

The collection of the data was carried out in a single visit by the doctor who regularly treated the patient. Thus, the data collected were the following: age of the patient, sex, period of development of the disease, presence/absence of rheumatoid factor, extra-articular manifestations, erosive disease, performance of a DXA, history of fragility fracture after the age of 50, the taking of corticoids, duration and dose, and treatment with bisphosphonates. Also collected in that visit were disease-modifying (DMDs)) and biological treatments. The patient completed the questionnaire on functional capacity – the Health Assessment Questionnaire (HAQ)[8]. The risk of fracture was quantified using a simplified FRAX® index using age, sex, smoking habit, history of fragility fracture after the age of 50, RA and the use of corticoids. The reason for using the simplified FRAX® index was the non-availability of all the necessary data, such as family history of hip fracture in forebears, alcohol consumption or early menopause. A weight and height of 60 kg and 160 cm, respectively, were established to obtain a BMI of 23.4 for all the patients.

The percentage of patients treated with bisphosphonates was analysed and the ACR criteria for the prophylaxis of corticoid-induced osteoporosis were applied[7]. In short, all postmenopausal women or those over 50 years of age with RA and corticoids are candidates for bisphosphonates, except those who have a risk of major fracture according to FRAX® of less than 10%, as well as a dose of less than 7.5 mg/d of prednisone, and who neither present osteoporosis by DXA, nor history of fragility fracture.

A descriptive statistical analysis was performed with parametric and non-parametric tests for comparison of groups. The differences between hospitals were analysed using Fisher's exact test. To analyse the factors associated with the use of bisphosphonates a multiple regression multivariate model was used with thoseparameters with statistical significance in the bivariate analysis. SPSS (Statistical Package for Social Sciences version 15.0) was used and the statistical significance was placed at $p<0.5$.

Results

The fieldwork was carried out between March 2013 and March 2014. 192 women were included, whose characteristics are set out in Table 1.

At their visit, 48% of the patients were receiving corticoids, with an average dose of 6 mg of prednisone (standard deviation – SD - 2.8 mg): 27% of the total were taking ≥5 mg for at least 3 months.

The average risk of fracture, measured by FRAX® in 185 patients was 8.2±7.3% for a major fracture and 3.55% for a hip fracture. In 149 patients (77%), the risk of major fracture was less than 10%, in 23 patients (12%) it was between 10% and 20%, while in 20 patients (10%) it was above 20%. The risk of hip fracture was higher than 3% in 46 patients (24%).

A DXA had been performed on 66% of the patients with a range according to hospital from 36% to 87% ($p<0.001$), the results being osteoporosis in 26%, low bone mass in 49% and normal in 24%. In comparison with those patients who had not had a DXA, the patients who had had the test more commonly had a risk of fracture >20% (3% vs 12%: $p=0.04$).

At the current visit 28% were receiving bisphosphonates, with a range of 14% to 39% depending on the hospital ($p=0.09$). Table 2 shows the patients in treatment with or without bisphosphonates, and the associated factors.

33 of the of the 88 patients (37%) in treatment with corticoids were taking bisphosphonates. 44 patients met the ACR criteria for OP prophylaxis, of whom 20 (45%) were taking bisphosphonates. 21 of the 30 cases (70%) with osteoporosis according to the DXA, and 12 of the 17 cases with a previous fracture (70%) were receiving bisphosphonates. In nine patients more than one of these conditions applied.

A significant association was observed between treatment with bisphosphonates and age, the duration of the disease, the average incapacity according to the HAQ, the average risk of fracture according to FRAX®, history of fragility fracture (OR 9.86; 95% CI: 9.26-10.47), treatment with corticoids (OR 2.49; 95% CI: 2.15-2.83) and the performance of a DXA (OR 9.59; 95% CI: 9.04-10.14) (Table 2). In the multivariate study, in which the variable dependent was the use of bisphosphonates, only the DXA ($p=0.03$) and history of fracture ($p=0.02$) were significant.

Discussion

The multicentre study which we present is a snapshot from real clinical practice of the approach to osteoporosis in patients with RA being monitored by a rheumatologist. A significant difference is observed in the request for DXA between the different hospitals, there being a less marked difference in the use of bisphosphonates. The ordering of a DXA is more frequent in patients at higher risk of fracture, a fact reported in a study of Japanese women with RA[9]. The use of bisphosphonates in our study was associated with the carrying out of a DXA and with history of fracture, but not with the risk determined by FRAX®, or with the use of corticoids after the multivariate study. Thus, slightly less than half of the patients with criteria for the prophylaxis of osteoporosis by corticoids were taking bisphosphonates, a similar figure to that reported in a North American study[10]. The guide of the Spanish Society of Internal Medicine recommends prophylactic treatment for corticoid-induced osteoporosis in postmenopausal women if they are going to receive, or are receiving, >5 mg/day of prednisone or equivalent for more than 3 months[6]. On their part, the consensus of the Spanish Rheumatology Society advises preventative measures in those patients who are going to take doses equivalent to ≥5 mg/day of prednisone for more than 3 months, reserving pharmacological treatment for those patients with a risk factor[4]. Neither consensus is specific to patients with RA.

In the CANAL study, which included female postmenopausal primary care patients with an average age of 63 years referred for DXA, the average FRAX® for major fracture was 6.1% in the subgroup from the Canary Islands[11], while in this study with RA the average FRAX® was 8.2%. The percentage of women treated in the Canarian group of the CANAL study was 28%, exactly the same as the patients with RA in this study, in spite of the fact that the risk of fracture in RA is higher. The results of our work suggest that in the absence of DXA, the prescription of bisphosphonates in RA is not appropriate since neither the risk of fracture nor the taking of corticoids are evaluated as they should be. Two studies have analysed the prescription of treatment for osteoporosis in women of all ages with RA, varying between 22% and 32%[12,13]. A Japanese study of 3,970 patients with RA found that only 44% of those with a high risk had been prescribed bisphosphonates[9], a similar figure to that in the north American CORRONA study[13], as well as in our study, in which 50% of women with a FRAX® higher than 10% were receiving bisphosphonates.

This study had various limitations: not all the risk factors for fracture were recorded, such as hip fracture of their forebears, alcohol, low weight, early menopause or other causes of secondary osteoporosis. Furthermore, the risk of fracture calculated by FRAX® is a simplification of the original. It has also been reported that other, simpler, tools may predict the risk of fracture in a similar way to FRAX®[14]. In any case, this simplified tool may always err due to its underestimation of the risk of fracture. On the other hand, we consider important the fact that our study includes a significant sample of patients being seen in five hospitals in real clinical practice.

In conclusion, in those patients with RA over 50 years of age in the Canary Islands the prescription of bisphosphonates by rheumatologists shows areas of improvement, especially in the evaluation of risk of fracture and in the prophylaxis of corticoid-induced osteoporosis.

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Conflict of interest: The first author, in the name of the other co-authors, declares that there are no conflicts of interest.

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Table 1. Characteristics of patients included. The data are expressed as n (%), unless indicated otherwise

		N valid
Average age, years: mean (SD)	62 (8)	192
Average duration of illness, age: mean (SD)	11 (8)	192
Positive rheumatoid factor	156 (81)	192
Erosive RA	97 (54)	178
HAQ: mean (SD)	0.96 (0.7)	188
Extra-articular manifestations (*)	31 (17)	182
Arthritis in remission for DAS28 (**)	72 (37)	172
Treatment with FAME (***)	179 (93)	192
Biological treatment	61 (31)	192
Treatment with corticosteroids	91 (48)	188
Current smokers	24 (12)	188
Fragility fracture after age 50	17 (9)	183
Performed bone densitometry	123 (66)	185
Treatment with bisphosphonates	52 (28)	186

(*) Pulmonary fibrosis or vasculitis or Sjögren syndrome or rheumatoid nodules.
(**) Disease activity index <2.6.
(***) Disease modifying drugs.

Table 2. Comparison of two groups of patients as a function of treatment with bisphosphonates

	Group bisphosphonate N=52	Group without bisphosphonates N=134	p
Age, mean (SD)	65.7 (8)	60.7 (7)	<0.001
Duration of disease, years, mean (SD)	14 (9)	10 (8)	0.02
Erosive RA, N (%)	35 (67)	65 (48)	0.06
HAQ, mean (SD)	1.23 (0.7)	0.84 (0.6)	0.001
FRAX® higher, average fracture (SD)	12.0 (9)	6.4 (6)	<0.001
FRAX® hip fracture, mean (SD)	5.9 (6)	2.4 (4)	<0.001
Treatment with corticosteroids, N (%)	33 (63)	55 (41)	0.04
Bone densitometry was performed, N (%)	48 (92)	74 (55)	<0.001
Fragility fracture, N (%)	12 (23)	4 (3)	<0.001

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Prevention of osteoporotic fracture in Spain: use of drugs before and after a hip fracture

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Summary

Introduction: Treatment of osteoporosis is focussed on the prevention fragility fractures, fractures of the hip being those which produce the highest rates of morbidity and mortality. The existence of a previous fracture is an important predictor of a new fracture.

Objective: we intend to analyse how treatment for osteoporosis varies before and after a hip fracture.

Material and methods: Using the 4,126,030 clinical records in the database for pharmaco-epidemiological research in primary care (Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria [BIFAP]) 2011 for the whole of Spain, information was obtained regarding patients who had a first hip fracture recorded between 2005-2011, having been monitored for at least a year before and after. We analyse the previous and subsequent treatment for osteoporosis (including calcium and vitamin D supplements).

Results: 2,763 patients over 60 years of age (average 81 years) had suffered a hip fracture, of whom 81.6% were women. Before the fracture 26.5% (95% confidence interval [CI]: 24.8-28.1%) had received some antiosteoporotic treatment, of which 12% (95% CI: 11.0-13.5%), were bisphosphonates. 38.6% (95%CI: 36.8-40.4%) received treatment after the fracture, 20.4% (95%: 18.9-22%) treated with bisphosphonates. The factors associated with the initiation of treatment after the fracture were being a woman, being younger and having a previous diagnosis of osteoporosis.

Conclusions: Most of the patients studied were not receiving preventative treatment before their hip fracture. After the fracture the prescription of treatment increased a little. The drugs most commonly added were calcium, vitamin D and bisphosphonates.

Key words: *osteoporosis, hip fracture, secondary prevention.*

Introduction

Osteoporosis is a bone disorder characterised by a deficit in both bone mineral density (quantity) and bone architecture (quality), which results in lower bone strength, greater fragility and a higher risk of fracture after minor trauma (fragility or osteoporotic fracture)[1]. According to the densitometric criteria proposed in 1994 by the World Health Organisation (WHO)[2], in Spain, the prevalence of osteoporosis is around 26% of women aged 50 years or over, increasing with age[3].

Among the osteoporotic fractures, vertebral fractures are those with the highest incidence, along with those of the radius, generating significant morbidity, although little mortality. But it is fractures of the hip, which appear later on, which present the greatest mortality[4], in addition to generating greater dependency and higher health costs. In a third of cases the patient had already had an earlier fragility fracture, with 21% of these even in the other hip[5]. A previous fragility fracture is, along with age, the most significant risk factor for suffering a new osteoporotic fracture. The appearance of a hip fracture due to a low impact trauma in older age permits the establishment with a high degree of suspicion of the diagnosis of established osteoporosis, making its confirmation through the use of other diagnostic measures, such as densitometry, unnecessary[6].

Currently, various drugs are used for the prevention of osteoporotic fractures such as the bisphosphonates (alendronate, risedronate, etidronate, ibandronate and zoledronate) strontium ranelate (which has recently seen its authorisation for use limited) estrogen receptor modulators (raloxifene and bazedoxifene), denosumab, teriparatide and parathyroid hormone. In the past, hormone replacement therapy or calcitonin were also used, but are now in disuse due to the existence of safer and more efficacious alternatives. The use of calcium[7] and vitamin D supplements[8] was also recommended, associated or not with the aforementioned drugs, to which have been attributed improvements in bone mineral density, whose efficacy in the prevention of fractures is currently compromised when used without being associated with other drugs[9].

The main aim of this study was to analyse, in a primary care setting, the prevalence of the use of pharmacological drugs for the treatment or prevention of osteoporosis before and after a first hip fracture of osteoporotic aetiology. The secondary aim was to analyse the possible factors associated with the decision to initiate treatment with bisphosphonates after a fracture in patients who were not taking them previously.

Material and methods

The study was carried out using the BIFAP database (Database for pharmaco-epidemiological research in primary care [Base de Datos para la Investigación Farmacoepidemiológica en Atención Primaria]) 2011, which includes anonymised information from the clinical records of 4,126,030 patients (with an average monitoring period of 4.8 years per patient), recorded by 2,239 family doctors and primary care paediatricians across the whole of Spain[10].

The computerised clinical history for each patient is composed of episodes, each of which has an associated diagnosis, coded according to the International Classification for Primary Care (ICPC)[11]. Each prescription issued for the patient is associated with a specific ICPC episode.

A study of transverse design was carried out of the use of medications for osteoporosis before and after a first episode of fracture. Those patients over 60 years of age with a first record of hip fracture coded as ICPC L75 in the period between 1st January 2005 and 1st January 20011, and with a record covering at least a year before and after the date of the fracture, were included. Those patients with a history of cancer and of Paget's disease were excluded.

For each patient selected, the sex, the age at the time of fracture, the date of the hip fracture and the presence of earlier diagnoses coded using ICPC corresponding to possible absolute or relative contraindications for the use of bisphosphonates, were noted from the medical record (Annex 1), as well as the presence of previous episodes of diabetes mellitus type 1, rheumatoid arthritis, hyperthyroidism, masculine hypogonadism, malabsorption, malnutrition, early menopause and osteoporosis (Annex 2).

The previous use of corticoids was also analysed, with, for the purposes of this study, a previous user being a patient who had had at least 3 prescriptions, and with an estimated 90 days or more of usage (based on the dosage) of prednisolone ≥ 5 mg/day (or equivalent) at any time before the date of the hip fracture.

Lastly, the use before or after the hip fracture of bisphosphonates (etidronate, alendronate, ibandronate, risedronate), vitamin D, calcium, calcitonin, estrogens, parathyroid hormones, teriparatide, raloxifene, bazedoxifene strontium ranelate and denosumab, were considered (Annex 3).

For each of the aforementioned drugs the patient was considered to be under primary prevention if they had received, at any time before the fracture, at least two prescriptions for one of the drugs listed, or in the case of having received a single prescription, if this was issued within 180 days before the fracture. The patient was considered to be under subsequent prevention for hip fracture if they had had at least one prescription of one of the drugs for osteoporosis described within a year after the date of the fracture.

In order to analyse which factors were associated with the initiation of treatment with bisphosphonates after a hip fracture in those who had not received earlier treatment, a logistical regression model was constructed, using as independent variables the year of the fracture, the age of the patient, the sex, the presence of diabetes, rheumatoid arthritis, record of osteoporosis or any contraindication for the use of bisphosphonates, as

well as previous exposure to corticoids. A backward selection strategy was used based on the likelihood ratio model for the selection of variables finally included in the model. For the descriptive analysis the proportion of patients who were receiving each of the treatments studied before, and in the year following, the fracture was calculated, as well as the average age and duration of the monitoring before and after the fracture, with corresponding confidence intervals of 95% (95% CI). For hypothesis testing regarding the differences in the proportion of use of each of the drugs before and after the fracture, the McNemar test for paired data was used.

Results

2,763 patients over 60 years of age (average of 81 years) were identified who had presented a first hip fracture in the period of the study, 2,225 of whom were women (81.6%). The average duration of the period of registration prior to the fracture was 5.8 years. The rest of the demographic and comorbidity data are described in Table 1.

A total of 731 patients (26.5%; 95% CI: 24.8-28.1%) had received one of the drugs analysed before the fracture (Table 2). Of these, 338 patients (12.2%; 95% CI: 11.0-13.5%) had received some treatment with bisphosphonates.

In the year following the hip fracture, 1,066 patients (38.6%; 95% CI: 36.8-40.4%) had received some antiosteoporotic treatment (Table 2), of whom 564 (20.4%; 95% CI: 18.9-22.0%) had received a bisphosphonate (Figure 1). The increase in the use of drugs against osteoporosis (p<0.0001), as well as the increase in the use of a bisphosphonate (p<0.0001) were statistically significant according to the McNemar test.

The most commonly prescribed drugs, both before and after the fracture, were calcium (23.2% and 32.4% respectively) and vitamin D (19.6% and 31.0% respectively). Among the bisphosphonates the most common were alendronate (6.6% and 10.4%) and risedronate (5.4% and 8.1%). On the other hand, it was notable that of the 508 men in the study, 11 (2.2%) were receiving alendronate before the fracture, and 29 (5.2%) took them within the year following the fracture.

Of the 338 patients who took bisphosphonates at any time before the fracture, 104 (30.8%) did not take them in the year after it. On the other hand, of the 2,425 patients who had not taken it before, 330 (13.6%) started treatment with bisphosphonates afresh in the year following the fracture. A total of 369 patients (13.4%; 95% CI: 12.1-14.6%) presented some absolute and relative contraindications for the use of bisphosphonates, including any diagnosis of gastritis or dyspepsia (complete criteria in Annex 1). Of the 642 patients who were taking calcium supplements at some point before the fracture, 31% (200 patients) did not receive them in the year after the fracture; while of 2,121 patients who were not taking them, 462 (21.8%) started to receive them after it. We obtained almost identical percentages with vitamin D supplements.

The logistic regression model (Table 3) regarding patients who were not taking treatment before the fracture (n=2,425) showed that the factors associated with a higher probability of initiating a treatment with bisphosphonates after fracture (n=330) were: being a woman (OR=2.44; p<0.0001), having a previous diagnosis of osteoporosis recorded (OR=1.61; p=0.009), being younger (OR per year of age=0.96; p<0.0001) and having some absolute or relative contraindication for the use of bisphosphonates (OR=1.41; p=0.033). No association was observed between the start of treatment with bisphosphonates after fracture and the fact of having diabetes, previous exposure to corticoids, history of rheumatoid arthritis or the year in which the fracture occurred. No significant interactions were observed between the independent variables analysed.

Discussion

The natural course of osteoporosis has a prolonged asymptomatic phase. In this period of primary prevention it is necessary to influence modifiable risk factors[12], although the use of drugs is controversial and the benefits, if any, are of low magnitude[13]. On the other hand, there is a consensus in not recommending population screening of bone mineral density with densitometry, and that this test is reserved for high risk cases and in order to take key therapeutic decisions[14].

After the first fragility fracture the risk of suffering future fractures increases considerably[15,16]. So, after a first vertebral fracture, the risk of a new vertebral fracture increases 4.4 times, and of a hip fracture by 2.3 times[17]. The usefulness of drugs for prevention subsequent to the fracture (which is usually called secondary prevention, but which would strictly be tertiary prevention),[18] has better tests available for its use in primary prevention[6,13].

Various studies have analysed the prescription of drugs for osteoporosis after a hip fracture, Some evaluate the treatment prescribed on discharge from hospital after a hip fracture, with levels of treatment which vary between 6%[19] and 19%[20]. Other works address treatment after any osteoporotic fracture over the course of a year, obtaining levels from 15% for treatment after the event[21], in other cases up to 24% after any fracture, with levels of 44% after vertebral fracture and 21% after a hip fracture[22]. In our case we obtained rates somewhat higher than the 38% for osteoporotic treatment, even though our data include treatment initiated up to a year after the fracture, and excluded patients with early mortality (with less than a year of records available after the fracture), which probably limits its comparability with other studies. The majority of the patients (73.5%) in our sample had not received drug treatment for osteoporosis before their hip fracture. After the first fracture, the doctors initiated some treatment afresh in a minority of patients, both with bisphosphonates (13.6%) and calcium-vitamin D (21.8%). By comparing the prevalence of its use before and after the fracture an increase was con-

Table 1. Description of the population. Clinical characteristics, exposure to corticoids and contraindications for the use of bisphosphonates, before a hip fracture

	n		
Total	2,763		
		Average	SD (min-max)
Age (years)		81.6	7.76 (60-105)
Preregistration period (days)		2,130	999 (366-10,909)
	n	Percentages	
Women	2,255	81.6%	
Diabetes mellitus type 2	454	16.4%	
Hyperthyroidism	30	1.1%	
Rheumatoid arthritis	32	1.2%	
Hypogonadism	0	0.0%	
Malabsorption	0	0.0%	
Malnutrition	4	0.1%	
Early menopause	5	0.2%	
Osteoporosis	428	15.5%	
Prior exposure to corticosteroids	144	5.2%	
Contraindications for bisphosphonates	369	13.36%	

firmed in the proportion of patients who received some drug treatment (from 26.5% to 38.6%), which was, furthermore, statistically significant ($p<0.0001$ for the McNemar test). In a north American study[23], the probability of receiving treatment after a hip fracture diminished from 40.2% in 2002 to 20.5% in 2011. Whether this increment is slight or not, is a matter of controversy, although the guides[6,15,17,24] include people with fractures as the target population, who obtain the greatest benefit from pharmacological treatment in normal clinical practice.

The highest consumption of antiresorptive drugs in our setting is found in women at relatively early ages (66 years on average)[25] in whom osteoporotic fracture is less frequent in comparison with the age group of older women, in which fractures are more common and (in the hip) more serious. However, a review concluded that alendronate does reduce clinically and statistically significantly vertebral, non-vertebral, hip and wrist fractures in secondary prevention, without there being statistically significant results for primary prevention, except for vertebral fractures[13], although this is a controversial point[26].

The logistical regression model allows us to analyse the factors related to the decision to initiate a treatment with bisphosphonates after a first hip fracture in patients who were not receiving them previously. The data suggest that doctors in primary care use criteria similar to those used for the initiation of treatment before fracture and in primary prevention. So, being female, younger and having an earlier diagnosis of osteoporosis increases the probability of initiating treatment after a first hip fracture.

Notable among the drugs which have most been used in our analysis, both before and after a fracture, are the bisphosphonates, alendronate and risedronate, similar to other series[27]. On the other hand there are the recommendations in the guides for efficacy, safety and price[10]. The data from the study showed the existence of men in treatment with alendronate; even though alendronate has shown definite efficacy in improving bone mass in males[28], its indication in the data

Table 2. Prevalence of pharmacological treatment for osteoporosis before and after a first hip fracture

	Before fracture (a)		After fracture (b)				
	n	%	n	%	Suspended (c)	Begin (d)	p (e)
Total	2,763		2,763				
Bisphosphonates (f)	338	12.2%	564	20.4%	104	330	<0.0001
Alendronate	183	6.6%	288	10.4%	84	189	<0.0001
Etidronate	21	0.8%	3	0.1%	18	0	<0.0001
Ibandronate	26	0.9%	74	2.7%	9	57	<0.0001
Risedronate	149	5.4%	224	8.1%	66	141	<0.0001
Calcium	642	23.2%	904	32.7%	200	462	<0.0001
Vitamin D	542	19.6%	857	31.0%	167	482	<0.0001
Ca + vitamin D	535	19.3%	828	30.0%	173	466	<0.0001
Calcitonin	91	3.3%	42	1.5%	72	23	<0.0001
Teriparatide/PTH	13	0.5%	58	2.1%	6	51	<0.0001
Estrogens	15	0.5%	6	0.2%	13	4	0.0490
Raloxifene/bazedoxifene	41	1.5%	17	0.6%	29	5	<0.0001
Strontium ranelate	21	0.8%	71	2.6%	14	64	<0.0001
Denosumab	0	0.0%	0	0.0%	0	0	<0.0001
In treatment (g)	731	26.5%	1,066	38.6%	194	529	<0.0001

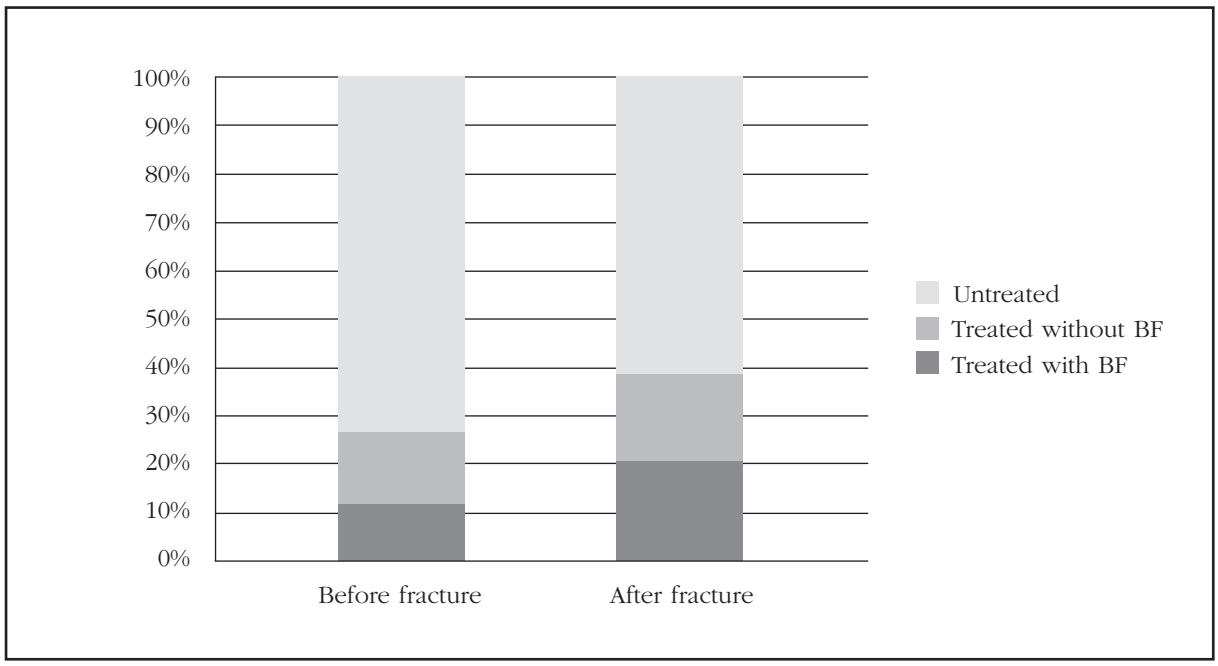
(a): at any time before the first hip fracture; (b): within the 365 days subsequent to the first hip fracture; (c): treatment stopped after the hip fracture; (d): treatment initiated after the hip fracture; (e): McNemar test for paired data; (f): in treatment with at least one bisphosphonate; (g): in treatment with one of the earlier drugs.

sheet is restricted to postmenopausal osteoporosis[29,30]. Only 15.5% of those patients with hip fracture had included in their diagnosis "osteoporosis", although they had received treatment with antiresorptive drugs, which suggests an additional problem of under-registration.

Our study has some limitations. It does not distinguish as to whether the treatment before the fracture was for primary prevention, given that the patient could have had a previous fragility fracture, as long as it was different from the hip. Neither does it analyse the dose or duration of the drugs used, since after the fracture there could have been patients treated for a short period, as against others who could have been treated for the whole period of the study after the hip fracture. The prescription of drugs subsequent to the fracture reflects the preoccupation by the professional with the risk of new fractures, which results in the initiation of treatment aimed at secondary prevention. However, it does not tell us about its persistence over time.

Another limitation is that, given the nature of the record from which the data was obtained, it is not possible to differentiate with certainty between absolute contraindications and precautions for the use of bisphosphonates. The association between the existence of an earlier contraindication before the fracture and the start of treatment after the fracture (OR=1.41) should be interpreted within this context. A possible hypothesis would suggest that the professionals, faced with precaution on use, don't initiate preventative treatment with bisphosphonates, but that once the fracture occurs, reconsider the risk-benefit balance in favour of pharmacological treatment. It is important to note that in our study only those patients with a survival of at least one year after fracture were included. This selection criterion adds consistency to our data and facilitates their interpreta-

Figura 1. Evolución del tratamiento antes y después de la fractura de cadera



tion, but makes it difficult to compare them with the results of other studies in which patients with early mortality after a fracture are included.

Notable among the strengths of the study is the high number of hip fractures analysed (n=2,763) and the variety of drugs studied. The fact that the clinical record was used as a source of data retrospectively, and the inclusion of treatment initiated up to a year after the date of the fracture, and not only immediately after it, means that the results are probably a good refection of real clinical practice in the primary care context. Using episodes of hip fractures in people over 60 years of age as a marker for established osteoporosis offers advantages since, given its gravity, it is not usually omitted from their record, and it rarely has a different origin from bone fragility[6]. Contrarily, the analysis of other types of fracture such as of the wrist or vertebrae are less specific, since they may have other origins, may pass unnoticed, or be variable in the register. A piece of data in favour of the external validity of the study is that the average age at fracture in our sample, 81 years, coincides with other Spanish studies with different methodologies, and coincides also in the ratio between women and men of 4:1[4,5].

The majority of patients in our study were not in treatment before suffering their hip fracture. After it there was a moderate increase in the prescription of drugs for osteoporosis. There are currently no data on the efficacy of these drugs in the prevention of hip fracture in patients who have already suffered a previous hip fracture, and it would therefore be very interesting to carry out new studies to determine whether the preventative treatment after a first hip fracture is effective or not in preventing new fractures.

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Table 3. Factors related to the initiation of bisphosphonate therapy after first hip fracture (a)

	OR adjusted (b)	IC 95%
Woman	2.44	1.69 - 3.52
Prior osteoporosis	1.61	1.13 - 2.30
Contraindication prior bisphosphonate (c)	1.41	1.03 - 1.94
Age	0.96	0.94 - 0.97

(a): logistical regression model with 2,425 patients who did not receive primary prevention with bisphosphonates prior to the fracture; (b): dependent variable: receiving secondary prevention with bisphosphonates in the 365 days subsequent to a first hip fracture; (c) absolute or relative contraindication for the use of bisphosphonates.

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Annex 1. Absolute or relative contraindications to the bisphosphonates

Gastric pathology:

- Oesophagitis: oesophagitis, caustic oesophagitis, reflux oesophagitis.
- Duodenal ulcer: duodenal ulcer, duodenal ulceration.
- Gastric ulcer: stomach ulcer, stomach ulceration, perforated stomach ulceration, gastrointestinal ulceration, peptic ulceration.
- Gastritis: disturbance in stomach function, dyspepsia, duodenitis

Annex 2. Other clinical characteristics analysed

- Hyperthyroidism
- Diabetes mellitus type 2
- Malabsorption syndrome
- Malnutrition
- Masculine hypogonadism
- Early menopause
- Rheumatoid arthritis
- Osteoporosis

Annex 3. Drug study

• Corticosteroids:	
H02AB01	Betamethasone
H02AB13	Deflazacort
H02AB02	Dexamethasone
H02AB09	Hydrocortisone
H02AB04	Methylprednisolone
H02AB06	Prednisolone
H02AB07	Prednisolone
H02AB08	Triamcinolone
• Vitamin D	
A11CC05	Cholecalciferol
• Calcium supplements	
A12AA01	Calcium phosphate
A12AA04	Calcium phosphate
A12AA10	Calcium glucoheptonate
A12AA12	Calcium acetate, anhydrous
A12AA20	Calcium (different salts in combination)
A12AA91	Calcium pidolate
A12AA92	Oseina-hydroxyapatite complex
• Calcium + vitamin D partnerships	
A12AX91	Calcium phosphate + cholecalciferol
A12AX92	Calcium lactate + cholecalciferol
A12AX93	Calciocarbonato + cholecalciferol
A12AX94	Calcium glucoheptonate + cholecalciferol
A12AX96	Calcium pidolate + cholecalciferol
• Estrogens	
G03CA03	Estradiol
G03CA04	Estriol
G03CA57	Conjugated estrogens
• Selective estrogen receptor modulators	
G03XC01	Raloxifene
G03XC02	Bazedoxifene
• Calcitonins	
H05BA01	Calcitonin (salmon, synthetic)
H05BA03	Calcitonin (human synthetic)
• Bisphosphonates	
M05BA01	Etidronic acid
M05BA04	Alendronate acid
M05BA06	Ibandronic acid
M05BA07	Risedronic acid
M05BA91	Alendronate acid + cholecalciferol
• Other endocrine drugs	
H05AA02	Teriparatide
H05AA03	Parathyroid hormones
• Other drugs bone diseases	
M05BX03	Strontium ranelate
M05BX04	Denosumab

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Gitelman syndrome and chondrocalcinosis. A clinical case review

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Summary
Gitelman syndrome is a tubulopathy of autosomal recessive inheritance which presents with, among other manifestations, hypomagnesemia and hypocalciuria. We present the case of a woman of 68 years of age who came for a consultation due to arthritis in the large joints, in the absence of other symptomology. The X-ray study showed deposits of calcium pyrophosphate in the knees, pubic symphysis and other joints. Blood tests revealed hypomagnesemia and hypocalciuria compatible with Gitelman syndrome, which was confirmed following a genetic study.

Key words: *Gitelman syndrome, chondrocalcinosis, hypomagnesemia.*

Introduction

Gitelman syndrome is a disease transmitted by recessive autosomal inheritance, and is caused by mutations in the gene SLC12A3, located in the 16q13 chromosome, which codes for the synthesis of the Na^+-Cl^- cotransporter of the distal convoluted tubule[1], which produces a defect in the reabsorption of sodium. This increase in the loss of salt, in turn causes a moderate volume depletion which activates the renin-angiotensin-aldosterone system[2]. It is a tubulopathy characterised by hypomagnesemia, hypopotassemia with metabolic alkalosis and hypocalciuria. In most cases it manifests itself in adolescence or in adulthood and follows a more benign course than what is known as Bartter syndrome[3]. Most patients have low or normal arterial tension and may present with signs of volume depletion[4]. Their levels of urinary prostaglandin E2 are normal. It is important to emphasise that the severity of the symptoms is not related to the genotype pattern, nor is there a correlation with the laboratory test results in these patients. The differential diagnosis should be carried out with diuretic or laxative abuse and with patients with chronic emetic syndrome[5-6]. In spite of the fact that the association between Gitelman syndrome and chondrocalcinosis has already been known for some years, only in rare cases are chondrocalcinosis and hypomagnesemia presented together, such as occurred in our patient, due to the accumulation of calcium pyrophosphate crystals in the joints stimulated by the hypomagnesemia.

Clinical case

A female patient, 68 years of age, with no pathological history of interest, who came for a consultation due to repeated episodes of pain and inflammation in both knees, attributed until then to a degenerative process, and which improved with non-steroidal anti-inflammatories. During the last two years she also had pain in both wrists and cervical spine of a mechanical nature. She said she had not suffered episodes of diarrhoea or vomiting, did not consume diuretics or any other type of pharmaceutical drugs.

The examination showed a patient in a generally good state of health, normohydrated, with blood pressure of 120/80 mmHg. The rest of the examination showed pain and flexion/extension limitation in the right knee with positive meniscal manoeuvres, without signs of leaking joints. The hands showed degenerative signs in the distal interphalangeal joints suggestive of Heberden's nodes.

In the analyses, the haemogram and formula were normal. The biochemical analysis showed the following results: urea, 37 mg/dl; creatinine, 0.71 mg/dl; glomerular filtrate, >60 mL/min/1.73m; total calcium, 9.45 mg/dl; inorganic phosphate, 3.51 mg/dl; alkaline phosphatase, 56 U/L; sodium(Na), 140 mEq/l; potassium (K), 3.4 mEq/l; TSH, 3.45 mUL; blood PTH, 2.9 pmol/L (1.6-6.9); 25-hydroxicolecalciferol, 30.9 ng/ml (30-100); bone alkaline phosphatase, 9.7 ug/L; magnesium (Mg), 0,54 mmol/L (0,66-0,99). In urine at 24 hours: negative proteinuria; calciuria, 69.56 mg (100-250); phosphaturia, 588.30 mg; Mg, 1.31 mg/dL (1.7-5.7); phosphate in the first urine of the day, 15.9 mg/dL (40-136). The acute phase reactants, rheumatoid factor, anti-citrullinated antibody and antinuclear antibodies (ANA, anti-ENA) were normal or negative.

The X-ray study showed calcification in the menisci of both knees with additional degenerative signs (Figure 1), of the pubic symphysis, of both carpi, in the hyaline coxofemoral cartilage, as well as in the metatarsophalangeal joint in the big toe of both feet (Figure 2).

The nuclear magnetic resonance (NMR) of the right knee showed severe degenerative signs of patellofemoral, and internal and external tibiofemoral osteoarthritis with degenerative rupture of both menisci.

A molecular genetic study was requested using PCR amplification and sequencing of the SCL112A3 gene, detecting homozygosis of the c2576T>C(p.L859P) mutation in the exon of this gene and which confirmed the diagnosis of Gitelman syndrome. The treatment consisted of oral supplements of magnesium at variable doses depending on the results of the monitoring analysis, and 0.5 mg colchicine a day to avoid episodes of pseudogout which the patent was suffering.

Discussion

Gitelman syndrome was described by this author in 1966. It is an autosomal recessive hereditary disease resulting from the mutation in the long arm of chromosome 16 in which the SLC12A3 gene which codes for the thiazide-sensitive Na-Cl cotransporter in the distal tubule is affected. Its incidence is one case in every 40,000 people[7].

In most cases the symptoms do not appear before the age of seven, and the disease is generally diagnosed during adolescence or adulthood with very light symptoms, in some cases even being asymptomatic, and whose definitive diagnosis has to be made through a genetic study, as with our patient[8].

The physiopathology of Gitelman syndrome is the disturbance of the function of the thiazide-sensitive ClNa cotransporter (TSC) which results in the tubular reabsorption of chloride and sodium in the distal nephron, causing a loss of salt and water, with the consequent hypovolemia. The reduction in vascular volume activates the renin-angiotensin system, promoting an increase in the concentrations of renin and aldosterone. This, in turn, facilitates in the cortical collector duct an increase in the reabsorption of sodium in the apical membrane and an activation of the Na^+-K^+-ATPase in the basolateral membrane. The increase in the concentration of aldosterone stimulates the H^+-ATPase in the cortical and medullar collector ducts, causing an increase in the secretion of H^+ in the apical membrane. At the same time, the urinary secretion of potassium is increased due to the

increase in the activity in in the basolateral membrane of the Na^+-K^+-ATPase. All this fosters the appearance of hypopotassemia alkalosis. The low intracellular content of sodium raises the tubular reabsorption of calcium through the activation of the Na^+/Ca^+ basolateral exchange, resulting in hypocalciuria. The magnesuria is increased by activating the Mg^{2+}/Na^+ exchange, given the existence of a negative transepithelial potential, which leads to the appearance of hypomagnesemia[9].

With regard to the renal function, a reduction in the renal tubular threshold for the reabsorption of magnesium without affectation of $TmMg^2$ is confirmed. These data are compatible with the fact that most of the filtered magnesium is reabsorbed in the thick ascending limb of the loop of Henle, and that the distal tubule only reabsorbs around 5% of the filtered magnesium. The mechanisms for concentration and acidification are intact. In the hydrosaline overload the distal absorption of chloride and sodium are reduced[10].

The molecular mechanisms which link the hypomagnesemia to the chondrocalcinosis are not fully understood. While it is known that magnesium is a cofactor for many pyrophosphatases, such as alkaline phosphatase, which allows, in turn, the conversion of inorganic pyrophosphate into orthophosphate. The magnesium also increases the solubility of the crystals of calcium pyrophosphate. In states of hypomagnesemia this solubility of the calcium pyrophosphatase is changed, and the precipitation takes place of the crystals in the joints producing a crisis of pseudogout and also reduces the natural dissolution of these pyrophosphate crystals[11,12].

In Gitelman syndrome the patients are frequently asymptomatic, except for the appearance of recurrent episodes of muscular weakness and tetany, which may be accompanied by abdominal pain, vomiting and fever. The intervals of apparent health may be very prolonged and the diagnosis is not usually established until adulthood. However, almost half of the patients present lesser symptoms such as an appetite for salt, fatigue, muscle weakness, general aching, dizziness, nocturia and polydipsia[6,10].

Figure 1. X-ray of the front of both knees. Intraarticular calcification

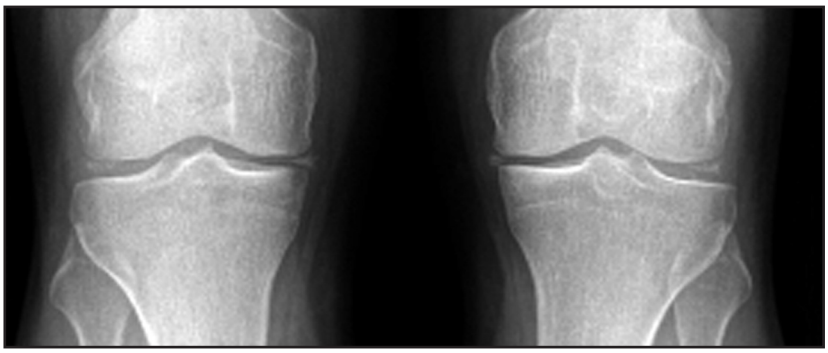
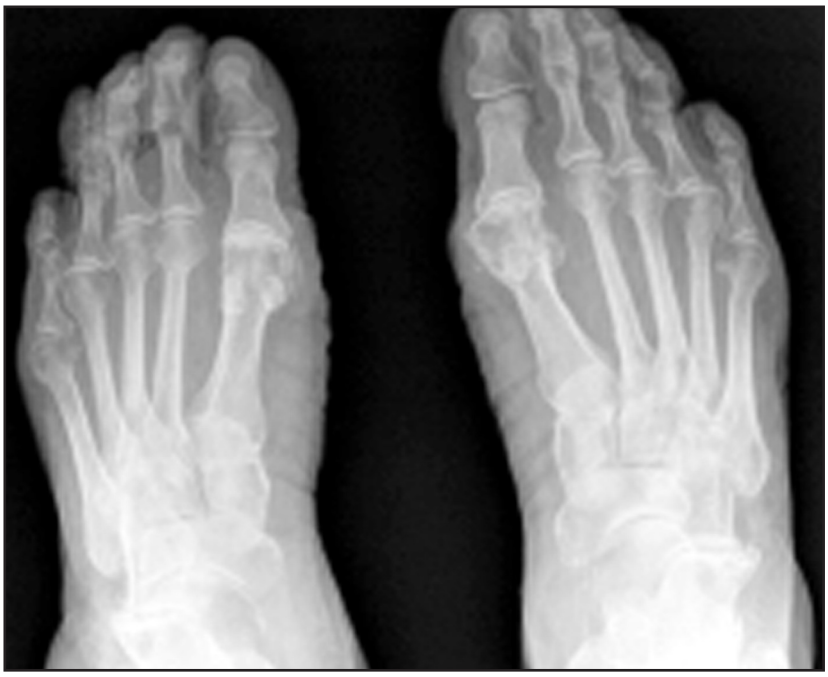


Figure 2. Plantar plate of the front of both feet. Metacarpophalangeal periarticular calcification



Our patient had presented different episodes of pain and inflammation of the joints, especially in both knees, although due to the fact that secondary evolved osteoarthritis was probably added to the chondrocalcinosis and degenerative rupture of both menisci in the right knee, its association with Gitelman syndrome was not suspected until low levels of magnesium in the blood and of calcium in 24 hour urine were observed, which was subsequently confirmed by the genetic study.

In the treatment of Gitelman syndrome, the efficacy of the administration of salts of Mg exclusively (preferably MgCl, which compensates for the loss of both Mg and Cl in the urine) has been demonstrated, with normalisation of the biochemical parameters and clinical remission. A correction of the hypopotassemia is performed occasionally with the administration of potassium salts.

Indomethacin or the potassium-sparing diuretics (spironolactone or amiloride) are reserved for the most refractory cases.

With the presentation of this case we consider the determination of levels of magnesium ions in the blood, as well as calcium and magnesium in 24 hour urine, to be important in all those patients with chondrocalcinosis and in those in whom hypomagnesemia is suspected, in order to exclude de Gitelman syndrome.

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Stress fracture in metatarsals: concerning two cases

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Summary
Stress fractures occur when a bone with normal elastic strength is subjected to higher loads than its mechanical strength. Although they may occur in any location they are more frequent in the metatarsals, these being the areas subject to greatest load. The clinical presentation for stress fractures is highly non-specific, which means that a detailed history is key to a suspected diagnosis. X-rays may be normal in the first stages, with gammagraphy and magnetic resonance being the gold standards for diagnosis in the initial stages. It is recommended that a study of possible underlying causes which may have contributed to the fracture is carried out. Generally the treatment is conservative, although in some cases, such as those occurring in the 5th metatarsal, surgical treatment may be necessary.

Key words: *fracture, stress, metatarsals.*

Introduction

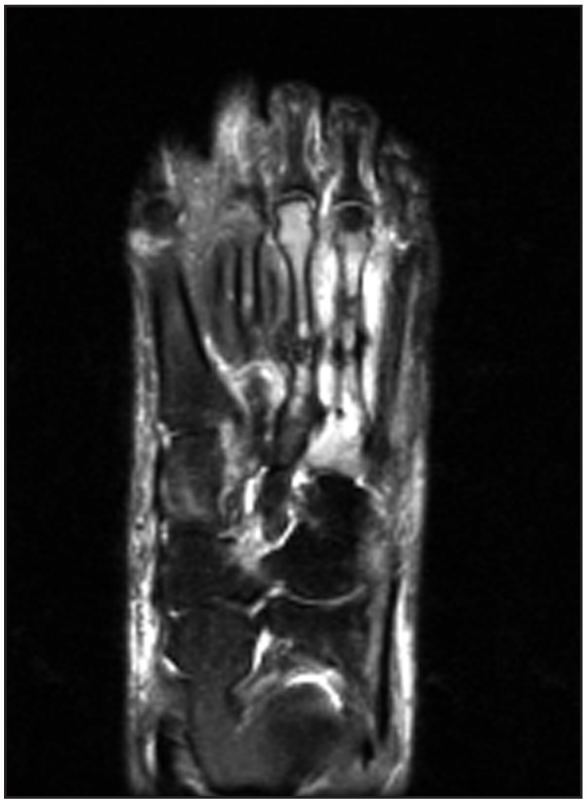
Stress fractures occur when a bone with a normal elastic strength is subject to repeated force by tension or compression. We need to differentiate between stress fractures and fractures due to insufficiency, which are those which are produced by physiological tensions on a bone with reduced bone strength.

Stress fractures may appear in any location, being more common in the metatarsals (MTT), mainly in the neck of the 2nd and 3rd MTT. The clinical presentation and physical examination permit a suspected diagnosis, confirmed with an X-ray. However, in the initial stages the X-ray may be normal or inconclusive, which means that the carrying out of a CT, NMR or bone gammagraphy is necessary. Below, we describe two cases of stress fractures.

Case 1

We describe the case of a female patient of 47 years of age being monitored due to psoriatic spondyloarthritis and fibromyalgia, in treatment with leflunomide, celecoxib and gabapentin, without history of interest and who maintained a regular menstrual cycle. She reported no toxic habits and her body mass index (BMI) was normal. In a routine examination she reported pain in her feet and ankles, with no history of trauma, with a mechanical rhythm, which had increased progressively until claudication occurred, with modification of the foot statics due to the pain. The examination highlighted the inflammation of the ankles and feet with pain from the pressure and bilateral fovea. An echography was carried out at the surgery which showed up a very marked inflammation of the subcutaneous cell tissue (SCT) with no signs of synovitis or Doppler signal. An X-ray was requested of the feet, which showed no pathological signs. Due to the significant SCT oedema, the patient was referred to angiology for assessment. From this service a lymphography was requested which confirmed severe bilateral lymphatic insufficiency. With the persistence of the symptoms of intense pain with claudication, the carrying out of an NMR of the feet was initiated, which showed in the right foot a fracture callus in the 3rd and 4th MTT and oedema in the 2nd MTT (Figure 1); and in the left foot a fracture line in the 1st MTT, and oedema in the 3rd and 4th MTT and in the surrounding tissue (Figure 2). Given the findings of the NMR, the patient was assessed by the traumatology service which indicated conservative treatment with non-weight-bearing and rehabilitation (magnet therapy). Due to the finding of multiple stress fractures, the study proceeded in our clinics, with analysis of renal function, calcium in blood and urine, ionic calcium, magnesium and PTH being carried out, which were normal. Only vitamin D was confirmed to be 19.5 ng/ml, for which treatment for supplements was indicated.

Figure 1. NMR image of right foot which shows fracture callus in the 3rd and 4th MTT (Case 1)



Assessing the case of this patient as a whole, we suggested, as a predisposing factor to the appearance of stress fractures, the significant antalgic alterations in foot statics which had developed due to the pain produced by the severe lymphatic insufficiency the patient had suffered.

Case 2

We describe the case of a 58 year old female patient. Her history includes a hysterectomy at 42 years of age due to metrorrhagia secondary to myoma. Two years before, she had been assessed by the gynaecology department due to densitometric lumbar osteoporosis (T-score in L1-L4 of -3, with normal figures in the femoral neck), treated with denosumab and vitamin D supplements. No toxic habits or personal or family history of fracture were reported, and her BMI was normal. She attended the clinic due to mechanical pain in the left foot, acute onset, without inflammation or triggering cause, which had increased in intensity until it became refractory to NSAIDs. In the examination there were no notable findings, except pain on the movement of the left forefoot. No alterations in the foot statics were observed. The patient was given an X-ray of the feet with showed no pathological signs. An NMR of the left foot was requested, which revealed a stress fracture in the 2nd MTT with periosteal callus and soft tissue oedema (Figure 3). An analytic study was carried out, which highlighted an increase in levels of PTH and vitamin D. (103.7 pg/ml and 272 ng/ml, respectively), attributed to an excess in the sup-

plementation of vitamin D. Renal function and calcium in blood and urine were normal. Treatment with vitamin D supplements and denosumab were stopped. Assessed by the traumatology service, conservative treatment was indicated, with non-weight-bearing, relative rest, NSAIDs and magnet therapy, with progressive improvement. Due to the age of the patient, 58 years, and the predominance of osteoporosis in the lumbar region, the patient was considered an appropriate candidate for treatment with SERMs (bazedoxifene), associated with supplements of calcium with vitamin D. One year later, in the same month in which the pain started in the earlier episode, the patient again reported the same symptoms in the left foot, without a triggering cause. An X-ray was requested which showed a callus from an old fracture in the 2nd MTT due to an earlier stress fracture, with no other findings. An NMR was carried out of the left foot to complete the study, which showed oedema in the 1st and 3rd MTT, cuneiform, scaphoid and astragalus bones, and posterior tibial tenosynovitis. A new bone densitometry was requested which showed a T-score in the lumbar spine of -3.5. The patient had not been taking bazedoxifene and vitamin D continuously, so the importance of resuming them was emphasised given that the levels of bone mineral density had worsened. The fractures were treated with rehabilitation and non-weight-bearing with progressive improvement.

Assessing the case overall, we suggest osteoporosis as the predisposing factor, since the patient was not obese, nor had she presented trauma or other risk factors. The fact that the two episodes of pain started in the same month (coinciding with a change of season) with a year's difference, appears to us striking. The patient reported no change in her habits or in her state of physical activity (sedentary) at these times, which is why we consider that the change in type of footwear may have put an overload on the left foot causing the appearance of new stress fractures.

Discussion

The first description of stress fractures are attributable to Dr Briethaupt, who studied pain in the feet of recruits which worsened with standing and training. Stress fractures are located in the MTTs in 25% of cases, this being the area of greatest load[1]. Those located in the 2nd, 3rd or 4th MTT are considered to be low risk because they usually respond to conservative treatment, while those in the 5th MTT are of high risk[2,3] since they may require more aggressive treatment[4,5]. Although different causes have been suggested risk factors are considered to be[6,7,8]: anatomical anomalies (flat feet, dorsiflexion or plantar flexion of MTT, contracted gastrocnemius, excessively long 2nd MTT); physical anomalies, obesity, osteoporosis and related diseases, lack of exercise, muscular insufficiency and external factors (footwear, changes in the intensity or amount of training, change in the training surface).

Figure 2. NMR image of the left foot with fracture line in the 1st MTT, bone oedema in 2nd, 3rd and 4th MTT, and in surrounding tissues (Case 1)

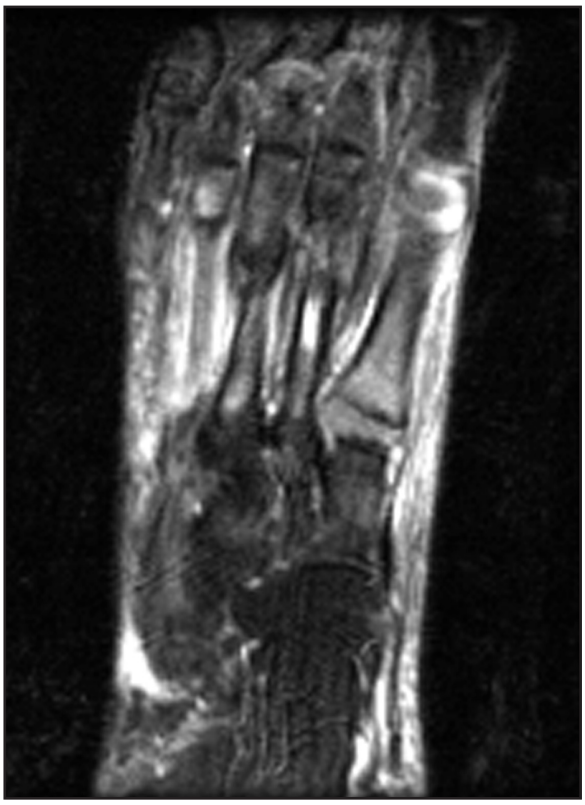


Figure 3. NMR image of left foot with fracture of 2nd MTT with periosteal callus and soft tissue oedema (Case 2)

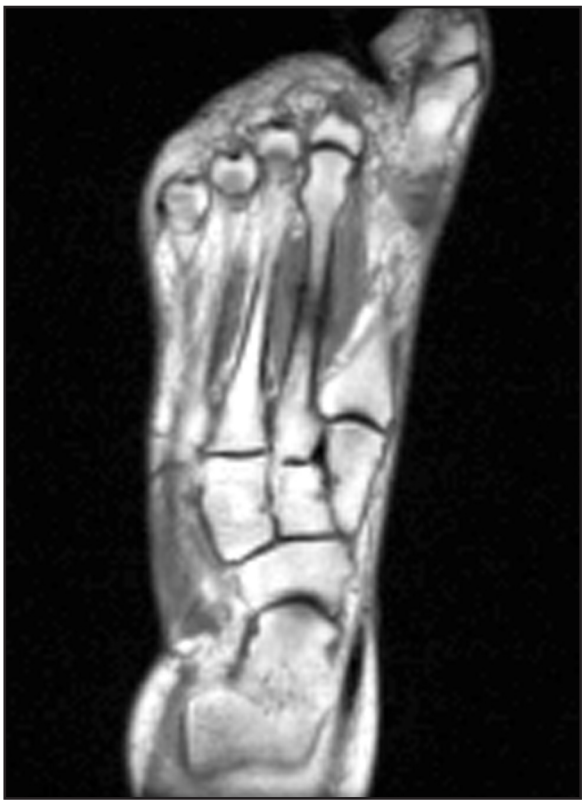


Table 1. Radiological gradation of stress fractures

	X-ray	Gammagraphy	NMR	Treatment
Grade I	Normal	Poorly defined hypercaptant areas	STIR positive T1 and T2 negative	3 weeks rest
Grade II	Normal	More intense capture but not defined	STIR and T2 positive T2 negative	Rest of 3-6 weeks
Grade III	Barely perceptible lines. Incipient periosteal reaction	Well defined areas of capture with well contrasted margins	T1 and T2 positives without cortical rupture	Rest for 12-16 weeks
Grade IV	Fracture or periosteal reaction	Intense transcortical capture	T1 and T2 positive with fracture line	More than 16 weeks rest

The diagnosis is based on a detailed clinical history which includes data on working and sporting habits. A stress fracture should be suspected in a case of foot pain which is poorly located and worsens gradually after the start of a new activity or very hard training weeks before the start of the pain. The radiological evidence does not usually appear before 2-6 weeks, cortical stretching and periosteal thickening and hypertrophy being the initial radiological signs. The degree of bone lesion may be of different intensity: bone contusion, cortical microfracture, extended periosteal microfracture and macroscopic transcortical fracture[9]. Gammagraphy and NMR are the "gold standards" for the initial diagnosis of cases, those in which X-ray tests may show normal findings. The classification of Arendt[10] correlates the histopathological studies with the imaging tests and treatment (Table 1). Grades I and II correspond to the stage of medullar oedema, grade III corresponds to periosteal changes and bone stress, and grade IV to clear cortical fracture.

The treatment is initially conservative, although in some cases, especially in fractures in the 5th MTT, surgical treatment may be necessary[11].

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Vitamin D and multiple sclerosis. Prevalence of hypovitaminosis D

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Summary

Multiple sclerosis (MS) is a chronic inflammatory autoimmune disease of the central nervous system whose etiology is unknown. Certain environmental factors, such as vitamin D, may have an influence on its pathogenesis, although the optimum threshold for vitamin D necessary to maximise its extraosseous benefits is not known. This article reviews, non-systematically, studies world-wide which relate vitamin D with MS. Overall, there are no significant differences between cases of MS and controls. In the case series, hypovitaminosis D with respect to values considered to be normal is seen in patients with MS, an observation which may also apply to healthy individuals. To be able to clarify the extent of the relationship between vitamin D and MS, further prospective studies are needed.

Key words: *vitamin D, multiple sclerosis, epidemiology, prevalence, deficit.*

Introduction

Multiple sclerosis (MS) is a chronic autoimmune disease of the central nervous system (CNS) triggered by an inflammatory disorder which causes focussed infiltrations of lymphocytes into the brain and spinal cord, causing demyelination and axonal damage over time[1]. Although we are able to establish a diagnosis of MS, its aetiology remains unknown. It appears that certain environmental factors may contribute to a susceptibility to this disease, without any one of them alone being sufficient to trigger it. Among those factors proposed are the geographical latitude of residence before puberty, which is associated with exposure to sun, and blood levels of vitamin D[2]. 1,25-dihydroxy-vitamin D ($1,25(OH)_2D_3$) is the form responsible for most, but not all, of the biological actions of vitamin D, while 25-hydroxy-vitamin D ($25(OH)D_3$) is the form most common in the blood[3], which is why it is this metabolite which is determined in most studies of vitamin D.

The importance of vitamin D for muscular-skeletal health and bone metabolism is widely known[4-7]. With reference to this, the optimum level of $25(OH)D_3$ in the blood has been established as being between 32-50 nM/L (12.8-20 ng/ml), this being the level associated with the maximum suppression of PTH[8]. According to the Institute of Medicine (IOM) of the United States, the recommendations regarding blood levels of vitamin D are that: values of $25(OH)D_3$ <30 nM/L are deficient; those between 30-50 nM/L may be insufficient for some people; and levels >50 nM/L are sufficient for nearly the whole population[9]. However, it is not completely clear what are the optimum levels necessary in relation to the extraosseous effect of vitamin D.

The prevalence of MS and its north-south gradient in the northern hemisphere is inversely correlated with exposure to UVB ultraviolet light[10]. However, this latitudinal gradient has been attenuated in the last 25 years, which suggests that environmental factors may play a determining role, exposure to sun and vitamin D being potential candidates which may explain this phenomenon.

This is because an inverse relationship between levels of vitamin D and the risk of developing MS has been observed, as well as which changes in lifestyle associated with lower exposure to sun and, therefore, less synthesis of vitamin D, may contribute to the attenuation of the latitudinal gradient[11].

The significance of vitamin D in relation to solar exposure dependent on the latitude of residence is due to the immunomodulatory properties attributed to vitamin D. The activated T & B lymphocytes have nuclear receptors specific to vitamin D, so that this vitamin increases the differentiation of the monocytes to macrophages and reduces the proliferation of activated lymphocytes, the synthesis of IgG by the B cells, the generation and activation of natural killer cells and the expression of various inflammatory cytokines, such as TNF-α, IL-1, IL-6 and IL-8[12].

In this article a non-systematic review is carried out of the literature to evaluate the prevalence of hypovitaminosis D in patients with MS in different regions across the world (Table 1), in search of a common pattern which could help us form a hypothesis for new lines of clinical research in this field.

Prevalence of hypovitaminosis in multiple sclerosis

Hypovitaminosis D is a phenomenon prevalent in southern Europe, the Middle East, India, China and Japan, on which the skin-type, sex, type of clothing usually worn, nutrition, the use of vitamin complexes, the body mass index and degree of urbanisation all have an influence[13]. These zones correspond according to latitudinal gradient with areas of average prevalence for MS, except the north of Europe, which would be a zone of high prevalence[14]. So, the question is, to what extent is hypovitaminosis D associated with MS as a causal factor, as a consequence, or simply an incidental finding which leads us to erroneous associations with this phenomenon.

Europe

In Europe, various studies have been carried out which have tried to determine the influence of blood levels of vitamin D on MS. Data taken from a transverse case-control study in Finland published in 2005[15] show that there are no differences in blood levels of $25(OH)D_3$ between the groups in the study, with average values of 50 nM/L for patients with MS and 57 nM/L for the controls. When the data is segmented according to whether the samples were taken during winter or summer months, there continues to be no statistically significant differences in the winter months (41 nM/L for MS and 44 nM/L for the controls), but the values were significantly lower in those patients with MS in the summer months (58 nM/L in MS vs 85 nM/L in the controls). A detail to be taken into account in this study is that the patients in the control group were not completely healthy, but that 65% were neurological patients without MS, but with diagnoses of Bell's palsy, hemiplegic migraine, migraine with aura, post-lumbar-puncture cephalgia, paraesthesia, paroxysmal positional vertigo, dizziness, central scotoma, extrapyramidal syndrome, depression, epileptic crisis and fibromyalgia. In addition, in Finland in 2008 another case-control study was published[16] with healthy controls drawn from laboratory staff, matched according to age, sex and place of residence. In this study it was observed that the seasonal variations in blood levels of vitamin D were the same for the patients with MS as for the healthy subjects. The average values obtained were 57.6±20.5 nM/L for those with MS and 55.3±22.4 nM/L for the healthy controls. Establishing a cut-off point of ≤37 nM/L, 43% of the patients with MS and 53% of the controls had a deficit of $25(OH)D_3$, while, if the cut-off point was set at 50 nM/L only 17% of the patients with MS and 22% of the controls had insufficient levels of vitamin D. Also in Finland, due to its high prevalence of MS, a study has

recently been published which studied blood levels of 25(OH)D_3 during pregnancy, and after, in patients with MS in comparison with healthy controls[17]. This study revealed that the patients with MS had lower levels of 25(OH)D_3 during the whole of the pregnancy compared with the healthy controls, with a striking decrease occurring in the first month post-partum. The authors described how this decrease was statistically significant in the group of patients with MS whose levels moved from 46.9 nM/L in the third trimester of pregnancy to 36.5 nM/L in the first month post-partum, and that 73% of the patients with MS had a vitamin D deficit, defined as <50 nM/L, during pregnancy. This was postulated to be related to a possible interaction between vitamin D metabolism and the hormonal state of these patients.

In Sweden, another Nordic country with a high prevalence of MS, a case-control study was published in 2012, subdivided into two groups, one consisting of patients with MS, matched 2:1 with their controls, and the other group consisting of pregnant patients matched 5:1 with their controls[18]. The results produced by this study show that the average blood levels of 25(OH)D_3 were similar between cases and controls, both in the subgroup of pregnant subjects (39 nM/L in the cases and 40 nM/L in the controls) and in the non-pregnant subgroup 40 nM/L in the cases and 39 nM/L in the controls). The study also confirmed the presence of seasonal variations, such that levels >75 nM/L were four times more frequent in the summer than in the winter.

There are authors who suggest that for hypovitaminosis D to have a real influence on the development of MS it needs to be present before the onset of the disease, meaning that if normal levels of vitamin D are maintained in the early stages of life, the risk of MS is reduced. For this reason, in 2014 a study was published, also carried out in Sweden, which tried to establish the risk of suffering MS according to the vitamin D status in the new born[19]. It was carried out in a cohort of all new born babies born in Sweden since 1975 and compared data from 459 cases and 663 controls at birth and of 298 cases and 307 controls at the start of the disease. The results obtained were that the vitamin D status at birth was not associated with the risk of MS in a wide section of the population of a city with moderate levels of sun. The values of 25(OH)D_3 at birth were 29.4 nM/L in the cases and 29.9 nM/L in the controls, at the point of diagnosis with MS, the blood levels were 65.0 nM/L for the cases and 67.8 nM/L for the controls, data which do not support the idea proposed to date of the role of vitamin D in the aetiology of MS.

In the Netherlands, the data available in relation to levels of 25(OH)D_3 in patients with MS are those from a prospective longitudinal study of 73 patients with relapsing-remitting MS published in 2012[20]. The average value of 25(OH)D_3 in this case series is 69 nM//L with a coefficient of variation of 41%. As in other similar articles, the seasonal variation in values of vitamin D follows a sinusoidal curve, and concludes that levels of 25(OH)D_3 <50 nM/L are associated with a 1.9 times higher risk of an exacerbation of the disease in an interval of 4 weeks compared with patients with levels >50 nM/L.

In Ireland, three cities are described with different prevalence for MS, which, from highest to lowest are: Donegal, Wexford and South Dublin. In 2011 a study was published regarding the prevalence of MS in Ireland, looking for an association between MS and vitamin D or genotype HLA[21]. The average value of 25(OH)D_3 was 38.6 nM/L in the cases and 36.4 nM/L in the controls, with no statistically significant difference. What was striking was that the levels of vitamin D were significantly higher in South Dublin (50.7 nM/L), which has the lowest prevalence of MS in Ireland, than in the two other cities (36.9 nM/L in Donegal and 39.7 in Wexford).

To demonstrate the possible involvement of vitamin D in patients with MS resident in Paris, a multicentre regional case-control study was carried out during the first quarter of 2010[22] which revealed lower levels of vitamin D in those affected by MS than in the control group, these being 14.5 nM/L and 16.7 nM/L, respectively. In another study carried out between June 2008 and February 2009[23] it was reported that 83% of the patients had insufficient vitamin D, defined as levels of 25(OH)D_3 <75 nM/L, and that 17% had a deficit of 25(OH)D_3, with an average value of 52 nM/L.

In terms of Spain, the data available to date are from a case-control study carried out in Cataluña which was published in 2012[24]. In this study, seasonal variations in blood levels of vitamin D were also reported, such that in the summer no statistically significant differences were found between the groups studied, but in the winter the results confirmed that the patients with relapsing-remitting multiple sclerosis (RRMS) had levels of 25(OH)D_3 lower than that of the controls (16.6 nM/L and 24.1 nM/L, respectively). However, this was not the case in patients with primary progressive multiple sclerosis (PPMS). These findings are simplified by the authors who conclude that in winter 65% of the patients with RRMS had insufficient levels of 25(OH)D_3 (<20 nM/L) in comparison with 45% of the healthy controls.

America

In America, the contribution made in 2006[25] by Munger et al. in relation to levels of 25(OH)D_3 and the risk of MS is notable. This was a case-control study carried out in seven million US military personnel, of whom 257 became cases of MS, and who were subsequently compared with two controls for each case of the same age, sex, race and date of taking the blood sample. It was observed that the average levels of 25(OH)D_3 were 75.2 nM/L in the white population, 29.7 nM/L higher than in the black population in which the average value was 45.5 nM/L, and 8.6nM/L higher than in the Hispanic population and other ethnic groups which had an average level of 66.6 nM/L. The study concluded that among white people the risk of developing MS

is reduced by 41% for each 50 nM/L increase in the level of $25(OH)D_3$, with no statistically significant differences between the sexes. In addition, it was observed that there was 51% less risk of MS among patients who had levels of $25(OH)D_3$ equal to or greater than 100 nM/L in comparison with those who had levels lower than 75 nM/L.

In New York a study was carried out and published in 1994[26] in which it was concluded that there was a high prevalence of vitamin D deficit and a reduction in bone mass in patients with MS. This study was carried out in 80 women with MS who were admitted to a tertiary hospital, without their being matched with healthy controls. The average blood levels of $25(OH)D_3$ in 52 samples obtained from this population was 42.9 nM/L without there being seasonal variations.

In California, another study on vitamin D and MS compared the blood levels in white patients with that of Hispanic patients, all of whom had already been diagnosed with MS, without healthy controls. This transverse study published in 2012[27] showed that the average levels of $25(OH)D_3$ were 32.1 nM/L among the Hispanic patients and 24.6 nM/L among the white patients, and that these levels did not experience seasonal fluctuations in the Hispanic population.

At the time of conducting this review regarding vitamin D in patients with MS there were no data from South America published in PubMed. Even in a publication by Brum in 2104[28] it is stated that there are no comparative studies on blood levels of vitamin D in Brazil's regions, although there had been studies in other selected risk groups such as postmenopausal women without MS[29].

Asia

We take as an example of the prevalence of hypovitaminosis D in Asia a study carried out in India published in 2013[30] which obtained average values for $25(OH)D_3$ of 39.0 nM/L in those patients with MS, significantly lower than the healthy controls who had levels of 45.5 nM/L. If only those patients who were in clinical remission (without exacerbations) were studied these levels would increase to 46.0 nM/L, while in those patients with exacerbations it was 37.0 nM/L.

Oceania

A study was carried out in Australia, published in 2011, whose aim was to evaluate whether exposure to sun and the state of vitamin D in the blood measured as $25(OH)D_3$ were associated with developing a first demyelinating event[31]. This was a multicentre case-control study with patients in four Australian cities: Brisbane, Newcastle, Geelong and the western district of Victoria, and in the island of Tasmania. For those patients who had had their first demyelinating event the average levels of vitamin D were 75.1.nM/L, and for the controls, 80.4 nM/L.

Another case-control study carried out in Tasmania and published in 2007[32] concludes that the average values of vitamin D were similar between the two groups studied, being 51.4 nM/L for the cases and 53.1 nM/L for the controls.

Prevalence of hypovitaminosis D beyond multiple sclerosis

Up to this point we have discussed how blood levels of vitamin D may have an influence on the overall increase in the epidemiology of MS due to its association with exposure to sun according to the latitudinal gradient. However, it is suggested that environmental factors such as lifestyle or dietary habits may be modifying factors which influence the prevalence of hypovitaminosis D across the globe.

The main source of vitamin D for most people is exposure to sun and the phototype of the skin, since the pigmentation related to melanin allows each person's skin to have sufficient vitamin D to satisfy their requirements. However, international recommendations which have been made in relation to exposure to sun to prevent skin cancer (avoiding exposure to the sun, clothing which leaves little skin exposed to the sun, sun protection…) has resulted in a world population at risk of hypovitaminosis D[33].

Reduced blood levels of $25(OH)D_3$ have been associated with other diseases apart from MS, such as cancer, cardiovascular disease, other autoimmune rheumatic diseases[3] and even with autism and cephalgia[34], as well as in the healthy population.

It is notable how populations which we previously assumed to be without vitamin D deficiency and healthy, may come to have low blood levels of 25-OH-vitamin D. This situation has been reported amongst medical students, researchers in health sciences and resident doctors due to their long working days without exposure to sun[35-38], as well as amongst inhabitants of urban areas which allow little access to sunlight[39]. But it is even more unlikely to find that individuals who appear to have adequate exposure to sun may also have reached reduced levels of $25(OH)D_3$, with average values of 32 ng/ml (80 nM/L), as is the case with surfers[40]. In any case, there are populations which, due to sociocultural or religious factors, have a high prevalence of hypovitaminosis D, such as has been reported in regions of Turkey and Morocco relating the clothing worn, this deficiency being higher among women[41], above all if the veil is worn, possibly dropping as low as 3.6 ng/ml (9 nM/L) in Turkey[42].

The importance of these findings is reinforced when we see that the blood levels of vitamin D are related to cardiovascular health[43-46], such that higher levels of $25(OH)D_3$ are associated with a reduction in the risk of cardiovascular disease, diabetes, metabolic syndrome and arterial hypertension, as well as in the risk of death, be it of cardiovascular origin, cancer[47,48] or due to other causes[49].

In the same way that vitamin D deficiency is considered to be an immunomodulatory factor in multiple sclerosis, as we reported at the start of this article, this effect has also been reported in other rheumatic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, lupus or Behçet's disease[50-54], in intestinal inflammatory disease and in coeliac disease[55-57].

Table 1. Levels of 25(OH)D_3 in patients with multiple sclerosis in different countries of the world

Author	Year	Country/ City	Sample size	25-OH-D_3 (nM/L)	25-OH-D_3 (ng/ml)	p value	Reference
Soilu-Hanninen	2005	Finland	40 cases / 40 controls	50 cases / 57 controls	20 / 22.8	0.202	(15)
Soilu-Hanninen	2008	Finland	23 cases / 23 controls	57.6 cases / 55.3 controls	23.0 / 22.1	0.81	(16)
Jalkanen	2015	Finland	15 cases 6 controls	46.9 antepartum - 36.5 postpartum 62.7 antepartum - 52.8 postpartum	18.8 - 14.6 25.1 - 21.1	0.02 0.54	(17)
Salzer	2012	Sweden	37 cases pregnancy (control 5: 1) 102 cases no pregnancy (control 2: 1)	40 cases - 39 controls 39 cases - 40 controls	16 - 14.4 14.4 - 16	0.99 0.97	(18)
Ueda	2014	Sweden	459 cases 663 controls	Neonates: 29.4 cases - controls 29.9 Debut: 65.0 cases - controls 67.8	11.8 - 12.0 26 - 27.1	>0.05	(19)
Runia	2012	Netherlands	73 cases	69	27.6	<0.05	(20)
Lonergan	2011	Ireland	632 cases / 632 controls	38.57 / 36.41	15.4 - 14.6	>0.05	(21)
Neau	2011	France	170 cases / 170 controls	14.5 cases / 16.7 controls	5.8 - 6.7		(22)
Pierrot-Deseilligny	2009	France	167 cases	52	20.8		(23)
Grau López	2012	Spain	40 cases RRMS 15 cases PPMS 40 controls	16.6 24.1 22.1	6.6 9.6 8.8	0.0001 0.7	(24)
Munger	2006	United States	148 caucasian cases 296 white checks 109 black / hispanic cases 218 black / hispanic controls	75.2 white 45.5 black 66.6 hispanic	30.2 18.2 26.6	0.001	(25)
Nieves	1994	New York	80 cases	42.9	17.2		(26)
Amezcua	2012	California	80 hispanic cases 80 caucasian cases	80.2 61.5	32.1 24.6	0.001	(27)
Pandit	2013	India	110 cases (63 outbreaks) 108 controls	39 46.5	15.6 18.6	0.003	(30)
Lucas	2011	Australia	216 cases / 395 controls	75.1 cases / 80.4 controls	30.0 / 32.2	>0.05	(31)
van der Mei	2007	Tasmania	136 cases / 272 controls	51.4 cases / 53.1 controls	20.6 / 21.2	>0.05	(32)

RRMS: relapsing-remitting multiple sclerosis; PPMS: primary progressive multiple sclerosis.

Conclusions

Vitamin D as an environmental factor influencing the pathogeny of MS is an increasingly accepted hypothesis in view of the existing evidence in this respect but, although its role in bone mineral metabolism is indisputable, it is still not completely clear what the threshold for vitamin D should be considered optimum to achieve its extraosseous benefits, among which is its immunomodulatory effect. On conducting this review to understand the state of hypovitaminosis D in the population with MS across the world we see that, overall, there are no statically significant differences between cases and controls[15,16,18,21,24,31,32]. One point to take into account is the correct choice of controls. For example, in a study by Soilu et al.[15], healthy controls were not selected, but controls unaffected by MS, and in the study by Nieves et al.[26] the cases were drawn from hospitalised patients, which means we already start with a series of cases with a higher degree of clinical affectation or other types of bias resulting from the hospitalisation itself.

In those studies in which only cases affected by MS were studied[20,23,26,27] the focus was on hypovitaminosis D with respect to the values considered normal for the general population, which are usually 20 ng/ml or 50 nM/L, but by not having healthy controls with which to compare them, it is not possible to attribute this observation to the disease itself, since we do not know if there are other factors involved such as lifestyle habits or clothing worn.

A study which concluded that there was hypovitaminosis D attributable to MS is that of Jalkenen et al.[17], which compared the situation pre- and post-partum in patients affected by MS and which observed how in the first month post-partum the drop in blood levels of vitamin D is clearly greater in the cases. The study by Pandit el al.[30] also showed that those patients with MS had lower levels of vitamin D than the controls, but it should be noted that approximately half of the cases were in clinical relapse at the time the sample was taken for the determination of vitamin D, which could mean a confusion factor since when only the subgroup without relapse was studied the average values of $25(OH)D_3$ were similar to that of the control group.

It appears that the clinical form of the disease influences the levels of vitamin D, as is described in the study by Grau-López et al.[24], which revealed that the primarily progressive forms had higher hypovitaminosis D than the relapsing-remitting forms, but only in the summer months. Another factor which seems to influence the prevalence of hypovitaminosis D in patients with MS, as described in the article by Munger et al.[25], is the patient's race, such that levels of $25(OH)D_3$ are higher in white people, followed by Hispanic people, with black people having the lowest levels.

What is still not clear after all this discussion is when is the right moment to avoid this hypovitaminosis. The study by Ueda et al.[19] is revealing with respect to this question. While the other studies discussed refer to a determination of a cross section, the Ueda study refers to a prospective cohort, in which those patients with blood levels of vitamin D lower at birth are those who subsequently most commonly develop MS. This observation reaffirms the importance of supplementing vitamin D in pregnant women as a measure of primary prevention, not only in MS but in as many other pathological situations where vitamin D has been seen to be involved. Thus we come to the dilemma – is hypovitaminosis a predisposing factor for MS, or is it a consequence of the disease? – since by being incapacitated they are less exposed to sun, and their fatigability increases with exposure to sun.

Taking into account the fact that most of the studies do not demonstrate differences between the cases and the controls, and that hypovitaminosis D exists in healthy individuals[35-42], could it be the case that vitamin D has an immunomodulatory effect only in individuals with a predisposition of suffering a particular disease? So, it seems that new, well-designed prospective studies will be needed in order to be able to glimpse in the future the extent and scope of the extraosseous effects of vitamin D.

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