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Alicizarin red staining of mineralization crops mesenchymal stromal cells differentiated into osteoblasts

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**METHODOLOGY AND DESIGN OF DATA**
Pedro Saaovedra Santana
José María Liminana Cañal
The Journal of Osteoporosis and Mineral Metabolism (Revista de Osteoporosis y Metabolismo Mineral) was first published in March 2009. It has now, therefore, completed its first five years. Born out of the need of the Spanish Society for Bone and Mineral Metabolism Research (Sociedad Española de Investigación Ósea y Metabolismo Mineral (SEIOMM)) to have its own official organ to disseminate its scientific activities, taking over this role from the Revista Española de Enfermedades Metabólicas Óseas (REEMO) given the insoluble difficulties which the management committee of SEIOMM then found in reaching an agreement with the editors of REEMO, both from an economic point of view and, more importantly, regarding the management of the Journal.

Starting from zero, the path to the present day has not been easy. In the field of scientific publications one of the most important questions, possibly the most important, is the dissemination of the articles and their visibility. Researchers send their best articles to the journals which have the best reach, and consequently, the greatest impact. In turn, the journals which publish high quality articles are the most cited, which leads to a virtuous circle. Inversely, journals having no impact face real hardship, since logically the articles they receive are less interesting and, therefore, will be cited less, which again completes the circle, but this time vicious.

From its early days we have been battling to ensure that the Journal of Osteoporosis and Mineral Metabolism is a quality publication. It has a committee of experts which brings together the best Spanish scientists in the field of mineral metabolism, an editorial committee of researchers of internationally recognised prestige, and our process of peer review, editorial rules and all the procedures for editing and publication of articles is very similar to those of other prestigious national journals in the medical arena, such as, for example, Medicina Clinica (Clinical Medicine). We also have a number of strong points, such as being free, both to publish and to read the articles on the web, and it is the only journal in the field of osteoporosis and mineral metabolism which is bilingual.

In addition, we have been successful in having the Journal of Osteoporosis and Mineral Metabolism in 16 bibliographic databases, and have requested fourteen others that we be evaluated for inclusion. Many of the databases in which we are included are highly prestigious, such as SciELO, DOAJ, or Google Scholar or Academic. However, our first attempt to be included in MEDLINE was rejected. One of the two main reasons was the relatively low number of original articles published each year, while the other was the practical absence of citations in other more prestigious publications indexed in MEDLINE or the Journal of Citation Reports (JCR).

After five years we are at a critical moment in the future of our journal. Its dissemination through the aforementioned databases allows us to believe that we are not invisible. Thus, if in Google we enter a search “Osteoporosis España” the fourth link which appears is the Journal of Osteoporosis and Mineral Metabolism. And if we enter “Osteoporosis and vitamin D” into Google Academic, the Journal of Osteoporosis and Mineral Metabolism is the second journal to appear.

There is still much to do, but now more than ever, it is necessary that all the associates of SEIOMM join forces to try to achieve the inclusion of the Journal in MEDLINE as a first priority, and then in JCR. We need to publish high quality articles, above all, so that articles in our journal are cited in other articles, we assume of greater quality, sent to high impact journals. These two tasks, sending articles and bibliographical citations in articles submitted to other publications, are in all our hands. These tasks are feasible and, since fortunately SEIOMM is a society whose members are notable for their hard work and production of research, it is solely a matter of wishing to do them.

We will continue to invest in our publication because we know that the Journal of Osteoporosis and Mineral Metabolism Research, and with it all the researchers of SEIOMM, has its place in international scientific dissemination.
Treatment adherence: a difficult, but not impossible, challenge

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The main aim of the treatment of a patient with osteoporosis is to avoid the appearance of osteoporotic fractures and, in the case in which it has already occurred, to avoid a new one. To achieve this it is important that in each specific case the risk of fracture is evaluated at the time and, as a function of its degree, low, medium or high, set out the preventive and therapeutic strategies necessary to reduce the risk of fracture in this specific person. One of the great challenges that still arises in daily clinical practice is to improve the adherence of patients to the various recommendations and treatments counselled by the health professionals. In 2003 the World Health Organisation defined “adherence” as the degree to which the conduct of the patient, in relation to the taking of medicine, the following of a diet or the modification of lifestyle, corresponds with the recommendations made by the health professional. This approach emphasises both the active participation of the patient and the responsibility of the health professional to create a climate of dialogue which facilitates shared decision-making, and contrasts with the concept of “compliance”, used as a synonym to adherence, which expresses the degree to which the patient follows the recommendations of the prescriber, and which implies that the patient has a passive role in their treatment, limited to taking the medicine as and when it has been prescribed to them. On the other hand, the term “non-compliance” blames the patient for their failure to follow medical instruction. The degree of adherence to pharmacological treatments for osteoporosis can vary between 40% and 80%; in general, it can be said that one out of every two patients is following their treatment a year after initiating it. The data for non-pharmacological recommendations are no better. The patients who have better levels of adherence and compliance have better final results, as well as in lower costs to the health system. Therapeutic adherence is a complex process which is influenced by many interrelated factors, among which are factors related to the patients (age, social problems, work, economic issues, level of education and training, beliefs, motivation,...), the disease (presence of absence of symptoms, depression, anxiety, personality disorders, memory loss, seriousness of the process, associated diseases, other treatments,...), the drug (dosage regime, complex treatments, high cost, secondary effects, non-acceptance of treatment, medium- to long-term effects, indefinite duration of treatment,...), the environment (existence of family problems, barriers to access,...) and the doctor (poor doctor-patient relationship, low patient satisfaction and/or low confidence in their doctor, feeling of not being listened to, feeling that they are not understood, changes due to generics,...). In the study by M. Sosa Henríquez and the Canarian working group on osteoporosis published in this number the degree of therapeutic compliance for osteoporosis was assessed in a population of women affected by the disease, with or without fragility fractures, treated by family doctors in a primary care setting. This study apparently suggests that patients with fracture take their treatment with greater adherence than those without, with rates of 75.9% versus 66.1%. The benefits in the prevention of new fractures in compliant patients, as compared with those who are not, has been evidenced in the literature. In a study by Caro et al. (2004) the compliant patients experienced 16% fewer fractures. The reasons which may account for this greater adherence to treatment which Sosa Henríquez et al. found in their study could be in relation to aspects of the patients’ psychology and lifestyle, such as a greater awareness of the disease after having suffered a fracture, fear of suffering a new fracture, having a desire to recover their health, family support, etc., and possibly a greater involvement of the health professionals caring for them, by intensifying the treatment interventions for patients at high risk of fracture, given a pre-
vicious history of fracture. Understanding the psychological determinants which improve therapeutic adherence, which are related to the aspects of the patients themselves, such as motivation, beliefs, self-caring behaviours, etc., are an interesting field of study which should be explored more in the future.

Another finding of this study was that a significant proportion of the patients (75%) received calcium and vitamin D supplements, observing that in women with treated fractures the percentage is greater than in those without fractures, 84.1% as opposed to 68.4% (p<0.001). One can contrast this high degree of adherence with other studies carried out in other Spanish populations. In a study carried out in health centres in Zaragoza only 29.3% of the population studied diagnosed with osteoporosis correctly followed treatment with calcium and vitamin D, with an appropriate frequency of withdrawal of prescriptions, and with almost half (42% of cases) not taking the treatment despite having an adequate prescription
t. In the study by Carbonell Abella et al. carried out in primary care health centres in the 17 autonomous communities of Spain only 52% received calcium and vitamin D supplements. In spite of the fact that calcium and vitamin D supplements reduce the incidence of non-vertebral and hip fractures in women with an insufficient intake of calcium and vitamin D, these patients frequently abandon them (secondary effects, poor tolerance, flavour, etc.). But is it possible to improve therapeutic adherence of patients with osteoporosis in normal practice? Given that therapeutic adherence is a complex problem, it requires demonstrably effective interventions, useful and feasible, taking a multidisciplinary approach in which professionals such as nurses and pharmacists can play a significant role in the interventions to be applied. Although different interventions aimed at improving adherence have been described, it is not possible to recommend a specific one which will serve in all cases, and it is possible that a combination of various interventions will be required (telephone calls, reminders, close monitoring, supervised self-monitoring, family therapy, psychological therapy, etc.)

An always essential first step is to assess the presence of possible predictive factors for subsequent non-adherence, such as insufficient understanding by the patient of the disease, lack of confidence in the benefits of the treatment, cognitive deterioration, concomitant psychological disorders, multiple coinciding treatments, complicated treatments, possible adverse effects, lack of a monitoring plan, poor doctor-patient relationship, difficulties in accessing treatment or cost of treatment. Interventions for the improvement of adherence should be discussed with the patient, taking into consideration their individual problems and needs.

Recommendations to be taken into account are:

- If a patient has a lack of adherence, investigate if it is intentional or not.
- Analyse the beliefs and worries of the patient regarding their medication.
- Carry out interventions aimed at specific problems: suggest to patients that they keep a record of taking their medicine, simplify the dosage regime, use pill boxes or similar, etc.
- If adverse effects occur, talk to the patients about the benefits and adverse effects, the long-term effects of the medication, the patient's preferences when managing the adverse effects, considering an adjustment to the dose, a change to another medicine or other strategies.
- Ask the patient if the cost of the medication poses a problem for them and consider options to reduce it.

It may also be worth using tools which allow an assessment at the start of the prescription of the probability of the treatment being followed in the medium to long term. Recently, a questionnaire has been developed specifically to evaluate adherence to osteoporotic menopausal medication in daily practice, called ADEOS -12. The questionnaire provides an adherence index which goes from 0 to 22. Values ≥20 are associated with a high probability of persistence, and an index of ≤16, a high probability of interruption of treatment in the following 9 months. However, it requires adaptation to, and validation for, our country Finally, health professionals should be aware of a new paradigm in relation to the management of chronic diseases, osteoporosis among them, which is to consider the central and significant role which the patient and their environment (family, community) have as co-participants responsible for the management of their disease. The active, informed patient participating in taking therapeutic decisions is a good ally in reaching an optimum level of adherence, to achieve the desired health outcomes.

**Declaration of conflicts:** The authors declare that there are no conflicts of interest.

**Bibliography**


Summary

Background: Fractures are a clinical complication of osteoporosis. Sufficient therapeutic compliance is necessary to reduce the risk of fracture. The literature suggests that a significant percentage of patients with osteoporosis soon abandon treatment, both drugs and calcium and vitamin D supplements.

Objectives: To study the degree of compliance with osteoporosis therapy in a population of women affected by the disease, with and without fragility fractures.

Patients and method: 413 women with a diagnosis of osteoporosis already established were included in the study consecutively, as they attended a health centre, without any selection or recruitment campaign.

Results: 38.6% of the women had suffered at least one fragility fracture, the most frequent being non-vertebral fractures as a whole, followed by vertebral fractures. Fractured patients had an average age 5 years older than those without fractures. The overall proportion of patients who were taking regular treatment was 66.1%, with the proportion of compliant patients being higher in those who had a fragility fracture, at 75.9% for those taking drugs in general and 84.1% for those taking calcium and vitamin D supplements, as against 59.7% and 68.4% respectively for those without fracture (p<0.001).

Conclusions: Those women affected by fragility fractures were older and had a greater adherence to treatment, both for drugs in general and for calcium and vitamin D supplements, than patients with osteoporosis without fractures. Non-vertebral fractures were those most commonly observed fractures.

Key words: osteoporosis, Primary care, fractures, treatment, compliance, calcium, vitamin D.
Introduction

Osteoporosis is a highly prevalent disease which may be treated by different medical specialists, including family doctors.

Primary care doctors form the base of the National Health System (Systema Nacional de Salud) and are the main point of access for patients1. The interest in and involvement of primary care doctors in the prevention diagnosis and treatment of osteoporosis is indicated both by the existence of working groups on this disease in their scientific societies, and by the scientific documents which they generate14.

However, there are questions regarding the treatment of osteoporosis which have not yet been resolved. One of these is that patients affected by osteoporosis and with fragility fractures are not indicated for treatment15. Another is that once indicated, the patients abandon treatment after a certain period of time, or do not follow the treatment correctly, which is to say that they have poor persistence or adherence1-4, which leads to an increase in the risk of fracture15-17.

We carried out this study in a population of patients previously diagnosed with osteoporosis and monitored by their primary care doctors, with the aim of understanding some of their clinical characteristics and the possible differences in their adherence to treatment, depending on whether or not they have fragility fractures.

Patients and methods

Context of study and selection of patients

All primary care doctors in all the health centres in the island of Gran Canaria participated in this study between 1st March and 30th September 2013. Their relationship is shown in Annex 1. The objective was to include 500 patients of both sexes affected by osteoporosis. In the end, 439 patients who met the inclusion criteria, and who had previously been diagnosed with osteoporosis, this diagnosis having been confirmed in their electronic primary care medical record, were recruited.

This study did not try to establish, confirm or question the diagnosis of osteoporosis, but this was accepted as an assumption, the diagnosis having taken place at another medical appointment. This could either have been in the primary care clinic of the same doctor, or through a referral to a specialist, either in specialist clinics (Centros de Atencion Especializada [CAEs]) or to a hospital, mainly the Bone Metabolism Unit of the Island University Hospital (Hospital Universitario Insular).

Each doctor included their patients in the study as they attended the health centre, either for monitoring or review, without any selection. After informing the patient of the objectives of the study their informed consent was requested to include their data in a questionnaire designed for this purpose, a modification of the Prochasa-Diclemente test15.

The study was approved by the ethics committee of the Mother and Baby Island Hospital (Centros de Atencion Infantil) and by the Medical Director for Primary Care of the Canarian Health Service (Dirección Médica de Atención Primaria del Servicio Canario de la Salud).

Statistical analysis

The data obtained from the questionnaire were entered into a database in the SPSS (Statistical Package for the Social Sciences) programme. In each of the groups, defined by the presence/absence of fractures, the categorical variables were summarised as frequencies and percentages, and the numerical variables by mean and standard deviation. The percentages were compared using the chi-squared test, and the means using the t-test for independent data. Those variables which showed significance in the univariate analysis were entered into a multidimensional logistic analysis. A retrospective selection of variables based on the verisimilitude ratio test was carried out. The resulting model was summarised as p and odd-ratio values, which were estimated with intervals of confidence of 95%. The contrast of hypotheses was considered statistically significant when the corresponding p value was lower than 0.05.

Results

A total of 500 patients participated in the study. Figure 1 shows the organogram of the patients who met the inclusion and exclusion criteria for this study.

Given the low number of males recorded, we decided to exclude them from our study, since we estimate that the results obtained when comparing such disparate sample sizes would not be very reliable.

In the end, 419 women were included, in whom we confirmed the existence of a fragility fracture in 166 (39.6%).

Table 1 records the clinical characteristics of the patients, classified according to the presence or absence of fractures. It was observed that the women with fractures were of greater age, an average of 5 years older than those without, 74 vs 69.8 years of age respectively, p<0.001. The time passed since the diagnosis of the osteoporosis was similar in the two groups.

Only 66.1% of the women affected by osteoporosis, with or without fractures, were receiving treatment for this disease at the point of consultation. From among those were treated, the women with fractures were a significantly greater proportion than those who had no fractures (75.9% vs 59.7%, p<0.001). The proportion of patients who received vitamin D and calcium supplements was higher than those receiving other drugs, with almost 75% of the women with osteoporosis receiving these supplements, the proportion of fractured women treated again being higher than those without fractures (84.1% with as against 68.4% of those without fracture, p<0.001).

With respect to the distribution of fractures, the non-vertebral fractures were the most frequent
(38.6%), followed by vertebral fractures, which made up 24.1% of the total of fractures. In this series 22.8% had had more than one fracture, whether they were vertebral or non-vertebral. Lastly, the most common non-vertebral fracture was the Colles fracture at 13.3%.

In carrying out a multidimensional logistic analysis (Table 2), we found that only 2 variables were statistically significantly associated with the presence of fragility fractures, which were age and the current consumption of calcium and vitamin D.

Discussion
Our study was aimed at trying to understand some of the clinical characteristics and degree of compliance with treatment in a population of patients of both sexes affected by osteoporosis in primary care. To achieve this, the design was intended to gather data from 500 patients diagnosed with osteoporosis, who attended the health centre for themselves. None of the patients were called to be included on the study.

We were therefore surprised by the low number of male participants, with only 20 out of a total of 500 included initially. This led us to exclude them from the subsequent statistical studies, since comparisons made between such disparate sample sizes seemed to us not to be reliable.

For us, this finding confirms one of the facts observed in the field of osteoporosis, which is that males are probably underdiagnosed and that they make up a smaller proportion of cases than women, in spite of the fact that osteoporosis affects, although not to the same extent, both sexes. The average age of all the patients with osteoporosis was 71.5 years. In addition, the women with fractures were older than those without (74 vs 69.8 years of age), all of which confirms that osteoporosis is a disease which affects older women, in whom, on our opinion, both preventative and therapeutic activities should be focused. Given that fragility fractures are a clinical complication of osteoporosis, treatment should be aimed at preventing its appearance, be it for the first time or as re-fractures. The achieve this aim, it is essential that patients carry out the treatment correctly, since no drug reduces completely the risk of new fractures and, furthermore, it has been observed that when patients do not take their medication correctly protection against fracture is reduced.

So, our findings are moderately optimistic since 66.1% of the patients with osteoporosis were receiving treatment at the time of completion of the survey, this being higher among those who had suffered a fragility fracture, reaching 75.9%, a statistically significant difference. Similar and even better results were observe with calcium and vitamin D supplements, with 74.6% of all those women affected by osteoporosis taking these supplements at the time of the interview, increasing to 84.1% in the case of patients with fractures, the difference again being statistically significant. Classically, it has been reported that patients affected by osteoporosis, in general, complied poorly with treatment, both with anti-resorptive drugs, especially the bisphosphonates, and with the anabolics, and in a more fundamental way, with calcium and vitamin D supplements. In some series it has been reported that the first thing that patients stop taking correctly is precisely calcium and vitamin D, which is exactly the opposite to what we found in our study, where 84.1% of the fractured patients took calcium and vitamin D, while only 75.9% took any other drug.

The patients had suffered a fragility fracture in 39.6% of cases (Table 3), and of these, the most common fractures were non-vertebral, which were recorded in 38.6% of these patients, followed by vertebral fractures (24.1%). We have separated the hip fractures from the non-vertebral fractures, and have grouped these in a different section since we believe that due to their mortality and morbidity they should not be included in the same group as, for example, fractures of the rib. We should highlight the fact that 22.8% of the patients had suffered various fractures, vertebral and non-vertebral combined.
Finally, the multidimensional logistic analysis, which is shown in Table 2, identified the variables associated with the existence of fractures within the population studied. We found, in first place, age, which is an all too well-known fact. Fragility fractures, even though they can be observed at any age, are more frequent the older the patient. The other data obtained was the current intake of calcium and vitamin D, which we believe is a consequence and not a cause, and that precisely due to their having suffered a fragility fracture the patients were better at taking the calcium and vitamin D treatment.

Our study has some limitations. Firstly, we could only include a small number of males, as has already been mentioned, having had, therefore, to restrict the study to women. Another limitation is not having estimated more precisely the adherence and persistence of the patients, using, for example the Morisky scale. And lastly, a description of the different drugs used was not included in the design of the study. However, one of its strengths is that we have been able to carry out one of the first co-operative studies between primary care, hospital care (Bone Metabolism Unit) and the University of Las Palmas Gran Canaria, which has enabled us to consolidate the Canarian working group on osteoporosis.

In summary, adherence to treatments for osteoporosis in the population studied, is acceptably high, and is higher in women who have suffered a fragility fracture.

Annex 1. Members of the Working Group on osteoporosis canary
Table 3. Distribution of fractures

<table>
<thead>
<tr>
<th>Fracture type</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertebral</td>
<td>40 (24.1)</td>
</tr>
<tr>
<td>Hip</td>
<td>24 (14.5)</td>
</tr>
<tr>
<td>Non-vertebrals*</td>
<td>64 (38.6)</td>
</tr>
<tr>
<td>Colles</td>
<td>22 (13.3)</td>
</tr>
<tr>
<td>Humerus</td>
<td>13 (7.8)</td>
</tr>
<tr>
<td>Other</td>
<td>29 (17.5)</td>
</tr>
<tr>
<td>Various**</td>
<td>38 (22.8)</td>
</tr>
</tbody>
</table>

* Includes those patients with a vertebral fracture than hip or.
** Included patients with multiple fractures of any type: vertebral, non-vertebral or hip.

Bibliography

Risk of fracture in the FRODOS cohort. Comparative study of the application of the Spanish, French, British and Swedish FRAX® models

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Summary

Background and objectives: Studies on the validation of FRAX® in Spain show an underestimation of the risk of principal osteoporotic fractures (POFs) and more accurate predictions for femoral fractures (FF). It has been suggested that this algorithm may be improved with more specific data on the epidemiology of these fractures in Spain. The objectives of this work were to describe the baseline risk of fractures according to the Spanish FRAX® model in the participants of the FRODOS cohort, and to compare these data with the application of other European models of FRAX® in the same cohort.

Methods: Observational study in a population cohort of 2,968 postmenopausal women (59-70 years of age). The online desktop version of FRAX® was used for multiple data entries to calculate the risk of POFs and FFs at 10 years using the Spanish, French, British and Swedish models in the same cohort.

Results: The lowest risk corresponded to the Spanish model: FF: 1.22% (36 expected fractures) and POF: 5.28% (n=197), while the highest risk was for the Swedish model: FF: 3.15% and POF 13.51% (n=401). The models for France and the United Kingdom had intermediate values.

Conclusion: In a Spanish cohort of 2,968 postmenopausal women the percentage risk of expected fractures at 10 years increased following a south-north latitude gradient when different European FRAX® models were applied. The results for the incidence of fractures on the FRODOS cohort predicted for the coming years will confirm, or not, the usefulness of this analysis.

Key words: FRAX, osteoporosis, risk of fracture.
Introduction
Osteoporotic fractures are one of the principal causes of morbidity in postmenopausal women in the industrialised nations.

If to this morbidity are added the predicted aging of the population and the exponential increase in the direct and indirect costs resulting from the diagnosis and treatment of osteoporosis, according to the assessment provided by models of health economics, it may be confirmed that this disease constitutes a significant public health problem.

It is for these reasons that for more than two decades various research groups have created different tools to optimise the diagnosis, calculate the risk of associated and secondary fracture, and improve the prevention and treatment of osteoporosis. One of the most widely-used tools is the FRAX index.

The FRAX model is a computer algorithm created for the prediction of the absolute risk of osteoporotic fractures at 10 years for men and women between 40 and 90 years of age. It is based on an arithmetic formula (not publicly available) which combines the weightings of different clinical risk factors, to which calculation it is possible to add, or not, values for bone mineral density in the femoral neck. Finally, all this is adjusted automatically to the rates of fracture and expected deaths for each country, according to the results obtained from the original cohorts. The expression of the risk of fracture is grouped into two categories: femoral fracture (FF) and principal osteoporotic fracture (POF), a category which includes femoral fracture, plus clinical vertebral fractures, proximal fractures of the humerus and Colles, or distal forearm fractures.

This model was developed under the auspices of the WHO at the Centre for Bone Metabolic Diseases at the University of Sheffield (UK), and used 9 different population cohorts (US, Asia, Australia and Europe including Spain). To date 58 models have been produced, adjusted for 53 countries, including most of the countries of Europe and North America, but also the other continents.

Studies evaluating the FRAX model in the Spanish population have tended to disagree, since expected fractures appear to be underestimated when compared to those actually observed, especially with the POFs, while the results for the FFs alone are more consistent. The hypotheses for explaining this disagreement, as suggested in an editorial specifically on this subject, would indicate that its principal cause is that the Spanish version for the calculation of risk at 10 years for POF uses data extrapolated from the original Malmö cohort (Sweden), while for the calculation of risk of FF, its own data was used. Other explanations for these disparities could be the different baseline risk for osteoporosis in each cohort, the loss of cases during follow up, as well as the small total number of fractures observed.

In spite of these drawbacks, the use of this index has become widespread, and has also generated Spanish studies which describe in an isolated way the prevalence of factors included in FRAX, the influence of the index at the point of prescribing drugs, or which compare the usefulness of this index with densitometry to calculate risk thresholds for fracture.

As already mentioned, the published results of research and the opinions of experts suggest that the Spanish version of FRAX could be improved. On the other hand, the underestimation of fractures observed compared with those expected using the index indicates that the epidemiology of the fractures in Spain would be closer to those of European countries with a higher incidence of fractures. For these reasons, we decided to apply the Spanish FRAX model to a prospective cohort from our country (FRODOS) and compare their results with those obtained by applying to the same cohort different European FRAX models such as those of France (as the closest country), of the United Kingdom (having an intermediate rate of fractures) and of Sweden (having the highest rate of fracture in Europe).

Methodology
The FRODOS (FRacturas Osteoporóticas De Osona) cohort, designed for the study of risk factors for fragility fractures, is formed of 2,968 postmenopausal women (aged between 59-70 at the time of recruitment) from the general population of the region of Osona (Barcelona). The FRAX risk was calculated using the baseline data of this cohort, created between the years of 2006 and 2008. The cohort is populational, the selection of the sample was randomised by municipality of residence and did not exclude participants under active antosteoporotic treatment, nor those with diseases which could have affected bone metabolism. The participation index was 71.1%, with 2,968 subjects out of a total 4,175 having been invited to participate. Information gathered from the women participating in the cohort included: a clinico-epidemiological questionnaire which recorded, among other things, all the FRAX variables, as well as lumbar and femoral dual X-ray densitometry (DXA), vertebral morphometry (MXA) and determination of the baseline for markers for bone turnover.

To calculate the risks at 10 years of POF and FF in Spain, France, the United Kingdom and Sweden the on-line desktop version of FRAX for multiple data entry was used, which allowed the entry of the original computerised database, and the performance of the required analysis. For each woman the estimated probability of POF and FF was calculated following the model for each country. The expected fractures were the result of the sum of the probabilities for each patient. The risk factors used to calculate this index were: age, weight, height, previous fractures (including the presence of morphometric vertebral fractures), family history (father or mother) of hip fracture, smoking habit, use of glucocorticoids, diagnosis of rheumatoid arthritis, alcohol consumption, bone mineral density (BMD) – T-score measured in the...
femoral neck and secondary osteoporosis, defined as the presence of at least one of the following pathologies: diabetes type 1, hyperthyroidism, premature menopause, malnutrition and chronic hepatopathy.

Statistical Analysis
A descriptive analysis was carried out in the sample, calculating the frequencies and percentages of each of the categorical variables. For the quantitative variables the mean and standard deviation were calculated. The statistical software package IBM SPSS Statistics version 20 was used for the analysis.

Results
Table 1 shows the baseline characteristics of the 2,968 participating women. To this information one needs to add the fact that 19% (n=563) were receiving some kind of antosteoporotic treatment. The mean age was 65.50±3.57 years, and body mass index 28.28±4.9 kg/m². One in five participants had an earlier fracture, and little more than 5% were taking oral glucocorticoids. 3.1% of the women were smokers and 0.5% had rheumatoid arthritis. Finally, 26.7% of the women (n=791) had osteopenia according to WHO criteria. The mean T-score in the neck was -1.18±0.98, which corresponds with osteopenia according to WHO criteria. The POF/FF relationship was 4.36 for Spain, France, the United Kingdom and Sweden. The lowest probability corresponded with the Spanish model, and the highest with the Swedish.

The POF/FF relationship was 4.36 for Spain, France and Sweden, while for the United Kingdom it was 5.98. Finally, the characteristics of the Spanish cohorts for which the FRAX® index is available are described in Table 3.

Discussion
This study describes in the Spanish cohort of FRODOS (a prospective cohort of 2,968 postmenopausal women) the clinical risk factors which the FRAX® model includes and the derived risk of suffering an osteoporotic fracture in 10 years. The innovative aspect is the comparison with the results of expected fractures not only applying the Spanish model but also the French, British and Swedish model to the same cohort.

For the creation of the FRAX® index, data from different prospective European, Asiatic and North American cohorts were used which included the analysis of events from more than a million people/year. The popularisation of this index is evident from the fact that its use has generated hundreds of articles, and FRAX® has been included in different guides to clinical practice.

However, while recognising the merits of this initiative for its daily clinical application, Siris and Delmas, already in 2008, also subscribed to the view that the importance of FRAX® would lie in formulating new health-economic strategies for the prevention and treatment of the risk of fractures in each country, even though the non-availability of adequate epidemiological data, and the use of derived or indirect data would increase the possibility of its inappropriate use.

The Spanish FRAX® model currently in use was created with Spanish mortality data and studies of the incidence of hip fracture carried out in Barcelona, Seville, Madrid, the Canary Islands, Cantabria and Zamora, while the calculation of the POF, with no Spanish data available, used the FF/POF relationship derived from the Malmö studies, which was 0.60 (6.98/11.6)°.

Without denying the merit of their having been the first works which recorded in an organised way the epidemiology of femoral fractures in our country, the representativeness of the Spanish cohorts included in the original development of FRAX® has been questioned, principally for not using in all cases population-based studies, but also due to the low number of individuals and events included, and the great variability in the incidence of fractures between the different autonomous communities of Spain.

Ideally, in order for a model for the prediction of clinical risk such as FRAX® to be used with confidence in daily clinical practice it ought to comply with at least two conditions: having demonstrated its validity in other population groups similar to the original ones; and helping to resolve problems for users less experienced in the field of osteoporosis, be they general practitioners or health care planners. It is evident that if the first point is not complied with there should not be a move towards the generalisation of its use since we would be doing this on an inappropriate basis. The Spanish FRAX® model has been evaluated in three cohort studies which clearly differ, but which, in having a sufficient number of participants and events, agree in their conclusions: the Spanish FRAX® model clearly predicts a lower number of POFs than are observed, while the prediction of FFs is somewhat closer to what actually happens; however, the predictive power measured by the area under the curve of the ROC curves is no higher than 70%. Other cohorts such as those from the ESOVAL study and our cohort, FRODOS are in the follow up phase and their results are expected in the next few years.

To obtain the results commented on in this work the software for multiple entries facilitated by the FRAX® licence was used, which avoided predictable errors generated by manual entry. In applying the Spanish FRAX® model to the FRODOS cohort the baseline risks of fracture expected at 10 years were 1.22 and 5.28% for FF and POF respectively. These results are lower than those reported in the ECOSAP study which were 3.67 and 8.78% respectively, slightly higher than those of the FRIDEX cohort, 0.95 and 3.88%, and similar to those of the Valencia group (1.9 and 5.5%).
while Tebé et al. reported only the risk for POF, which was 4.6%. These disparities and similarities may be explained mainly by the different average ages, which is to say, the higher the age the higher the risk, and vice versa, while the cohorts with average ages of around 65 years had intermediate results.

On the other hand, the asymmetric prevalences of the risk factors may also add to the explanation of these differences.

In applying the French model of FRAX® to our cohort, chosen for geographic proximity and epidemiological similarity, risks for FF of 1.54% and for POF of 6.64% were found. Although these probabilities are slightly higher than those found with the Spanish model, the results are superimposable at confidence interval of 95%. However, the application of the British model does increase slightly the possibility of FF, duplicates the prediction of POF, while the Swedish model shows nearly a three-fold increase in the prediction of both types of fracture. It is worth remarking that the FF/POF relationship was 0.23 in the Spanish, French and Swedish models, while in the British it was 0.16. This would confirm that the Spanish and French models apply the aforementioned Swedish formula, while the British model would use its own formula.

To try to overcome the absence of FRAX® models, in some areas applications from other countries have been used with their local cohorts. In Poland the British model was used in a study of 500 women to evaluate an overestimation in predictions, while a study carried out in Denmark applied the Swedish tool with an excellent correlation between events observed and predicted. On the other hand, a recent update of the Italian FRAX® model revealed notable changes in the risks for FF, and thus, in the FF/POF relationship. In the discussion the authors indicate the importance of having coherent data and models.

Thus, in the search for new options to improve the understanding of the epidemiology of osteoporosis in Spain and increase the options for strategic approaches to this pathology, we present the baseline risk of expected fractures in our cohort using the Spanish FRAX® model, along with a comparative exercise by applying the models of other European countries. These results will see their true relevance when compared with the incidence of fractures in the coming years.

Table 1. Baseline characteristics of the women in the cohort FRODOS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean ± SD</td>
<td>65.50±3.6</td>
</tr>
<tr>
<td>BMI (kg/m²), mean ± SD</td>
<td>28.68±4.9</td>
</tr>
<tr>
<td>Previous fracture, n (%)</td>
<td>646 (21.8%)</td>
</tr>
<tr>
<td>Family history of fracture, n (%)</td>
<td>659 (22.2%)</td>
</tr>
<tr>
<td>Smokers, n (%)</td>
<td>92 (3.1%)</td>
</tr>
<tr>
<td>Consuming alcoholic beverages, n (%)</td>
<td>42 (1.4%)</td>
</tr>
<tr>
<td>Treatment with glucocorticoids, n (%)</td>
<td>167 (5.6%)</td>
</tr>
<tr>
<td>Rheumatoid arthritis, n (%)</td>
<td>15 (0.5%)</td>
</tr>
<tr>
<td>Secondary osteoporosis, n (%)</td>
<td>791 (26.7%)</td>
</tr>
<tr>
<td>T-score femoral neck, mean ± SD</td>
<td>-1.18±0.98</td>
</tr>
</tbody>
</table>

Declaration of interests: The authors declare that there are no conflicts of interest.

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Bibliography

Table 2. Expected fracture at 10 years in the cohort according to different models FRODOS

<table>
<thead>
<tr>
<th>Model</th>
<th>Spain</th>
<th>France</th>
<th>United Kingdom</th>
<th>Sweden</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>% (IC 95%)</td>
<td>n</td>
<td>% (IC 95%)</td>
</tr>
<tr>
<td>MOP*</td>
<td>157</td>
<td>5.28 (4.5-6.1)</td>
<td>197</td>
<td>6.64 (5.7-7.5)</td>
</tr>
<tr>
<td>FF**</td>
<td>36</td>
<td>1.22 (0.8-1.6)</td>
<td>46</td>
<td>1.54 (1.1-2.0)</td>
</tr>
</tbody>
</table>

* Major osteoporotic fractures.
** Femoral fractures.

Table 3. Baseline characteristics of participants in the Spanish cohort and their FRAX® assessment

<table>
<thead>
<tr>
<th>Model</th>
<th>n</th>
<th>Age, mean (SD) (Min - Max)</th>
<th>Risk MOP</th>
<th>Risk FF</th>
</tr>
</thead>
<tbody>
<tr>
<td>FRODOS*</td>
<td>2,968</td>
<td>65.5±3.6 (59-70)</td>
<td>5.28%</td>
<td>1.22%</td>
</tr>
<tr>
<td>ESOSVAL**</td>
<td>5,310</td>
<td>64.3±9.3 (&gt;50)</td>
<td>5.50%</td>
<td>1.90%</td>
</tr>
<tr>
<td>ECOSAP**</td>
<td>5,201</td>
<td>72.3±5.3 (65-100)</td>
<td>8.78%</td>
<td>3.67%</td>
</tr>
<tr>
<td>TEBE ET AL.**</td>
<td>1,231</td>
<td>56.1±7.8 (40-90)</td>
<td>4.60%</td>
<td>-**</td>
</tr>
<tr>
<td>FRIDEX**</td>
<td>770</td>
<td>56.8±8.0 (40-90)</td>
<td>3.80%</td>
<td>0.95%</td>
</tr>
</tbody>
</table>

* Current results.
** Unpublished data.
Normal values of the aminoterminal propeptide of type I collagen (PINP) and the isomer beta I collagen carboxyterminal telopeptide (\(\beta\)-CTX) in serum of healthy premenopausal women of the Community of Madrid

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Summary

Introduction: In the laboratory it is sometimes difficult to find the normality intervals of the population itself, there being a tendency to give the normality value specified by the manufacturer of the reagent. The aim of this work was to calculate the normality values for aminoterminal propeptide of type I collagen (PINP) and for the beta isomer of carboxy-terminal telopeptide of type I collagen (\(\beta\)-CTX) in the blood of a group of premenopausal women from the autonomous Community of Madrid.

Materials and methods: The study was carried out in 50 healthy premenopausal women between 27 and 40 years of age (mean ± standard deviation of 34±3 years, working in a hospital and a pharmaceutical laboratory in Madrid.

Blood levels of PINP and \(\beta\)-CTX were determined using the technique of electrochemiluminescence (Elecsys, Roche).

Results: Normal values of 36.2±12.9 ng/ml (range 10.4 to 62) for PINP and 0.306±0.121 ng/ml (range of 0.064 to 0.548) for \(\beta\)-CTX were obtained.

Conclusions: Although the population sample used was small and localised, we consider that these values may be used as the normality interval for Spanish women.

Key words: normality interval, PINP, \(\beta\)-CTX.
Introduction
The use of markers for bone remodelling in clinical practice raises the necessity of having appropriate and reliable normal values with which the patient data may be compared. The aim of this work was to calculate the normality values for aminoterminal propeptide of type I collagen (PINP) and for the isomer beta carboxy-terminal telopeptide of type I collagen (β-CTX) in the serum of healthy premenopausal women of the Community of Madrid (Spain).

Materials and methods
The study was carried out in 50 healthy premenopausal women of between 27 and 40 years of age, with the mean ± standard deviation of 34±3 years, staff of the Jiménez Díaz Foundation Hospital and the offices of a pharmaceutical laboratory in Madrid. All the subjects completed a short questionnaire to discount bone metabolism diseases, hypothyroidism or diabetes, as well as taking a haemogram and basic biochemistry which included thyroid hormones. None of the subjects were taking oral contraceptives. The blood was taken in fasting, at between 8 and 10 in the morning. The blood was centrifuged and the serum separated and immediately frozen aliquots were stored at -80ºC for the analysis of bone markers.

The PINP in the serum was determined by the electrochemiluminescence technique using the Elecsys (Roche) automatic method. The sensitivity of the method is 0.01 ng/ml and the inter- and intra-analysis variation coefficients are <1.8% and <4.3% respectively.

The β-CTX in serum was also determined through electrochemiluminescence using the same Elecsys (Roche) method. The sensitivity of the method is 5 ng/ml and the inter- and intra-analysis variation coefficients were <2.1% and <2.4% respectively.

Results
Values (mean ± SD) of 36.2±12.9 ng/ml (range: 23.3–49.1) were obtained for PINP and 0.306±0.121 ng/ml (range: 0.185–0.427) for β-CTX (Table 1). Figure 1 shows the values of the quartiles corresponding to each marker.

Discussion
 Following the criteria of other researchers such as Richard Eastell, we consider that the normality range for markers for remodelled bone should be that of healthy premenopausal women of between 30 and 45 years of age, who have already reached their peak of bone mass, since although bone remodelling activity increases postmenopause, the aim of antiosteoporotic treatments is to return the patients’ remodelling activity to premenopausal levels, and preferably to its first quartile1.
Due to the small differences which may be seen in different geographic areas, it appeared interesting to us to compare the values obtained in our work with earlier studies carried out in Spanish women.

Thus, the values of PINP we obtained are similar to those found by Álvarez et al.\(^2\): average value 33.8 ng/ml in the control group of healthy postmenopausal women, although using a different method (radioimmunoanalysis – RIA of Orion Diagnostica). Using the same technique, Peris et al.\(^3\) reported values of PINP in serum of 30±11 ng/ml in a group of healthy premenopausal women. As can be seen, the values found using RIA are slightly lower than those obtained by electrochemiluminescence in our work: 36.2±12.9 ng/ml.

As was expected, the values found in a group of healthy postmenopausal women are higher than those for premenopausal women, since bone remodelling accelerates in the postmenopausal state. Thus, Martínez et al.\(^4\) reported average values of 47.7±19.9 ng/ml in a group of 1,080 healthy postmenopausal women, and Schoppen et al.\(^5\) found average values of 40.9±12.6 ng/ml in a group of 18 women who were also healthy and postmenopausal.

With respect to levels of \(\beta\)-CTX, our values are similar to those found by Kanterewicz et al.\(^6\) in a population of 34 premenopausal women: 0.305±0.150 ng/ml, obtained using the same method used in our study (Elecsys, Roche). Martínez et al.\(^4\), in the aforementioned work found levels (0.387±0.197 ng/ml) higher than ours in a group of 1,080 healthy postmenopausal women, and it was the same case with values obtained by Schoppen et al.\(^5\): 0.47±0.14 ng/ml in the group of 18 healthy postmenopausal women.

**Conclusions**

Given the similarity to those found by other authors in our country, we consider that the values of PINP and \(\beta\)-CTX (36.2±12.9 ng/ml and 0.306±0.121 ng/ml, respectively) obtained in this work may be safely used as normality values for these markers for bone remodelling in Spanish women.

**Bibliography**

Migratory arthralgia and sclerosing bone lesions. Differential diagnosis

Summary

Osteopokilosis is a rare benign bone dysplasia that may result in musculoskeletal pain, although it is usually asymptomatic. It is frequently suspected and diagnosed by the incidental finding of characteristic bone lesions on plain radiographs requested for another reason. Identifying these lesions and ruling out other possible causes is crucial to carry out a correct differential diagnosis and to avoid unnecessary invasive studies. We describe a case of a patient 32 years old who was referred to our rheumatology department because of joint pain.

Key words: sclerosing bone disorders, sclerosing bone dysplasias, osteopoikilosis, osteosclerosis, sclerotic bone metastases, radiography, diagnosis.
Introduction

Osteopoikilia or disseminated condensing osteopathy is a benign bone dysplasia related to an anomaly in the endochondral maturation process. Clinically, it is usually asymptomatic, although the patients may present with joint pain, skin alterations, various developmental anomalies or other associated pathologies. The bone metabolism-related laboratory parameters are usually normal, and the diagnosis is usually made as a result of the incidental discovery in radiological studies of characteristic bone lesions. The radiological images typically show multiple radiodense bone lesions, of small size, rounded or oval, distributed in the periarticular regions of the long bones. Understanding and indentifying the radiological patterns which characterise the different bone pathologies is, along with the clinical history, fundamental to carrying out a precise diagnosis.

Below, we describe a clinical case of a patient admitted due to articular pain.

Clinical case

A woman of 32 years of age was admitted for a rheumatology assessment in relation to migratory arthralgia worsening after exertion during the last two years. The articular pain disappeared with non-steroidal anti-inflammatories. The patient did not suffer from any systemic disease or take any pharmacological treatments. In the physical examination slight pain was reported with the passive abduction of both shoulders, and pain on palpation of both pertrochanteric regions and the right wrist. No tumefaction was found, or limited movement in any joints. No cutaneous lesions or other anomalies were found. The laboratory studies carried out (haemogram, transaminase biochemistry, renal function, alkaline phosphatase, calcium, phosphorous, thyroid hormones and parathyroid hormone, electrolytes, proteinogram, VSG, C-reactive protein (CRP), 25(OH) vitamin D, markers for bone resorption, calcitriol in urine at 24 hours, antinuclear antibodies (ANA), rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), and hepatitis B and C serology) were normal.

In the X-rays there was evidence of multiple small, rounded, sclerotic bone lesions, distributed symmetrically bilaterally, and located in the head of the humerus, the periarticular section of the scapula (Figure 1), metacarpals and phalanges of the hands, pelvis, acetabulum, femoral head and condyle (Figure 2), proximal and distal thirds of the tibia and in the bones of the foot. No affection in the cranium or vertebral bodies was observed. The bone gammagraphy with technetium showed no pathological radiotracer deposits. The patient was diagnosed with osteopoikilosis on the basis of the clinical findings, the normality of the laboratory parameters and the characteristic X-ray images.

Discussion

Osteopoikilia or osteopoikilosis is a hereditary bone dysplasia of unknown etiology, related to an alteration in the resorption of the secondary spongy bone tissue and in the normal formation of trabeculae along the tension lines during the process of endochondral maturation. A pattern of dominant autosomal inheritance has been identified, although sporadic cases have also been reported. There is a similar incidence in both sexes, with an estimated prevalence of 1/50,000 inhabitants. The patients frequently remain asymptomatic, which means that the diagnosis can occur at any age, on the incidental discovery of the typical radiological lesions in X-ray studies requested for other reasons. These bone lesions appear during embryonic development and in infancy, and usually remain throughout the patient’s life, although both increases and decreases in their size, and even their disappearance, have been reported. However, not infrequently patients have manifestations of the condition such as pain or joint leakage (15-20% of cases), or cutaneous lesions (25%). Connective tissue nevi are the most common cutaneous lesions, followed by the tendency to develop keloids and sclerodermiform lesions. The coexistence of dermatofibrosis lenticularis disseminata, a hereditary connective tissue disorder characterised by the appearance of fibromatose papules (nevi) on the back and the extremities, and osteopoikilia, called osteodermatopoikilosis or Buschke-Ollendorf syndrome. Patients with osteopoikilosis may also have stenosis of the medullar canal, anomalies of the cranoe-cervical hinge (Klippel-Feil syndrome), cranoe-facial and dental alterations, syndactyly, growth anomalies (dwarfism), renal or cardiac malformations, urogenital defects, endocrine pathologies (early pubescence) and autoimmune rheumatological conditions, aortic coarctation and other vascular problems. The articular clinical condition may be related to the osteopoikilia itself or to associated autoimmune diseases such as systemic erythematous lupus, rheumatoid arthritis, spondyloarthropathies or familial Mediterranean fever. Although our patient reported joint pain which worsened in various locations with activity, there were no signs which suggested the coexistence of an associated systemic pathology, either in the physical examination or in the complementary studies carried out. Neither were cutaneous alterations or other anomalies detected.

The X-ray images characteristic of osteopoikilosis show multiple small osteosclerotic lesions, which may vary from being millimetres to centimetres in size, of homogeneous density and morphologically, generally rounded or oval. These lesions have a typical periarticular distribution, usually located in the metaphysis and epiphysis of the long bones. In up to 90% of cases they appear in symmetrical bilateral form. The small bones of the hands and feet (phalanges, metacarpals, metatarsals, the carpal and tarsal bones), the pelvis, the femur, the cubit, the radius, the sacrum, the tibia, the fibula, the scapula and the proximal section of the humerus are the bones most commonly affected. The X-ray images from our patient showed the typical rounded radiodensi-
se lesions distributed periarticularly and located in the humeral and femoral heads, the scapula, the pelvis, the femoral condyles (Figures 1 and 2), the proximal and distal thirds of both tibias and bones of the hands and feet. The location of these lesions in the cranium, ribs or the vertebral bodies is not normal, except in osteomesopycnosis, a variant of osteopoikilosis characterised by the presence of irregular sclerotic lesions located in the vertebral bodies, close to the edge of the vertebral end plates. There seems to be a close relationship between the alterations underlying the different bone dysplasias, which makes it impossible to differentiate them histologically on some occasions. Furthermore, those patients with osteopoikilia frequently display other dysplasias such as enostosis, osteomas, striated osteopathy, melorheostosis or multiple exostosis. The histological study of lesions in patients with osteopoikilosis shows, as with enostosis, condensations of compact lamellar bone (sclerotic areas) located in the spongy bone, consistent with the radiological findings. The coexistence of alterations which suggest the presence of osteopoikilosis, striated osteopathy and melorheostosis in the same patient is known as mixed sclerosing bone dystrophy. As with other bone dysplasias, those patients with osteopoikilia have an increased risk of pathological fractures, although there is no evidence or any anomaly in the process of bone scarring following fractures.

Occasionally, the neoplastic degeneration of some of the osteosclerotic lesions has been reported, especially in the direction of chondrosarcoma and osteosarcoma. A bone gammagrapy with 99m technetium-MDP is usually normal in patients with osteopoikilosis, and carrying it out may help to differentiate it from other processes such as blastic metastasis or to identify a malignant transformation of the lesions. However, the presence of an anomalous focus of radiotracer captation does not exclude this dysplasia, since some large lesions during growth, especially in young patients, may show this alteration. In our case, no hypercaptation of the radiotracer was observed in any location.

The diagnosis of this bone dysplasia is usually made from the typical osteosclerotic lesions in the X-ray images. Other complementary studies are not usually required and the need for a bone biopsy is exceptional, a tool limited to those cases in which there is diagnostic doubt or suspicion of neoplastic degeneration. Numerous pathologies of different degrees of severity and prognosis have been linked to the presence of sclerosing bone lesions. Blastic metastases are the most common cause of multiple radiodense bone lesions in adults, notable both for their incidence and their seriousness. Breast neoplasia in women and prostate carcinoma in men are the tumours most commonly associated with them. Bone metastases are generally asymmetrical, variable in size, and have a predilection for the axial skeleton, the ribs and the diaphysis of the long bones. On rare occasions they appear in the carpal or tarsal bones.
Radiologically, they are characterised by the presence of bone destruction and periostic reaction, as well as by the finding of numerous captation foci in bone gammagraphy\(^1\). On the other hand, various congenital and/or hereditary pathologies have been associated with the appearance of osteosclerotic lesions throughout a patient’s period of growth, notable of which are the heterogeneous osclerotic lesions which, combined with the clinical history, offer characteristic radiological patterns which, combined with the clinical history, are usually sufficient to make a correct differential diagnosis and to establish a precise diagnosis. In conclusion, we consider that the evaluation of patients with joint pain associated with multiple osteosclerotic radiological lesions should be carried out exhaustively, taking in to account the possible pathologies involved and discounting the related diseases which may be coexistent. Understanding the different radiological patterns is essential in order to make a correct differential diagnosis, and to avoid diagnostic errors or the unnecessary use of invasive tests. Blastic metastases are a challenge for which the performance of a bone gammagraphy with 99m Technetium-MPD may help resolve\(^7\).

Finally, a regular assessment of patients with osteopoikilosis is recommended due to the risk of malignant transformation described.

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Finally, a regular assessment of patients with osteopoikilosis is recommended due to the risk of malignant transformation described.

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Finally, a regular assessment of patients with osteopoikilosis is recommended due to the risk of malignant transformation described.

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