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Our Journal

Dear members:

It is an honour for the Management Board of SEIOMM to present to you the new journal of our Society –*Revista de Osteoporosis y Metabolismo Mineral*– which is going to take forward the difficult mission of replacing the Spanish Journal of Metabolic Bone Diseases, which, for reasons known to you all, is no longer our official journal.

From the start the new journal will be six-monthly and will contain the classic contents of a scientific publication. *Revista de Osteoporosis y Metabolismo Mineral* is born to last, and will provide a quality channel through which work by the specialists who make up SEIOMM can be published. Original articles, reviews, clinical notes… will all have a place in the new publication, in which you will also be able to find news of the activities of our Society and its working groups. The annual calendar of publication will be completed by a third issue per year dedicated to bringing together the material presented at our annual Conference, and there is also the possibility of our producing extraordinary editions on current themes of interest to our scientific community.

In order for it to gain the maximum distribution and to reach the greatest number of specialists, the publication of the journal will consist of a printed edition –in Spanish– only distributed to SEIOMM members and subscribers. An on-line version will also be published –revistadeosteoporosisymetabolismomineral.com– in Spanish and English, in indexed PDF format. From the web page of the journal its contents can be viewed and then downloaded in Spanish or English. SEIOMM and the publishing company Ibañez & Plaza SL will also promote links between the web page of the journal and those of other scientific societies and bodies. Similarly, from the appearance of this first issue the necessary steps will be taken to include *Revista de Osteoporosis y Metabolismo Mineral* in Free Medical Journals and, in time, in the principal medical databases.

The new journal belongs to SEIOMM and is, therefore, a journal for all its members, OUR JOURNAL. This is the feeling we would like to convey. From now on we are already seeking your help, which could be to send us original articles or reviews, to collaborate by acting as a reviewer, or simply in sending us your ideas and suggestions. And, you will be reassured to know that –as we had hoped– that your response has been excellent. Enough material has already been submitted to fill a number of issues, and you can be sure that the work of the authors and reviewers will allow us to improve the contents from issue to issue. So, with help from all who have supported SEIOMM, in a short time we will have an established, indexed, and above all, quality journal which reflects the research carried out by our Society.

The Management Board of SEIOMM

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Epidemiology of Paget's disease of bone in an area of Barcelona

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Summary

Paget's disease of bone (PD) is a focussed disorder, asymptomatic in the majority of cases and of an unknown etiology. The epidemiology of this disease is little characterised; its global prevalence or incidence in Spain is not known. The objective of this study is to determine the prevalence and incidence of PD in an area of the city of Barcelona (Barceloneta) which has a health care system in which primary, hospital and specialised care are integrated, and in which digitised archives of complementary investigations, diagnoses and treatments are available.

Patients and Methods: The population of the area of Barceloneta is 18,509 inhabitants (1996 Census) with 6,989 people older than 55 years. The process fro the identification of patients affected by PD in the area of Barceloneta was carried out through a review of the digitized archives of diagnoses, treatments, analyses, pathological anatomy, and bone radiography and gammagraphy from the primary care centre (CAP), the Rheumatology service and other services of the Hospital del Mar. In cases detected the diagnosis was confirmed through a review of the clinical history by the researchers.

Results: 16 patients were found to have the disease (10 women and 6 men). The average age was 79.2 years (range 65-92). Monostotic/Polyostotic: 8/8. Symptomatic/Asymptomatic: 9/7. The apparent prevalence in the population over 55 years of age was 0.23%. In the period 1996-2000, five new cases were diagnosed, the incidence being 1.78/10,000 person/years. Assuming that only 20% of cases are symptomatic is it is possible to infer that the total number of patients is 45, real P being calculated at 0.64%.

Conclusions: In the area of Barceloneta (Barcelona, Spain), the real prevalence calculated is 0.64% and the estimated incidence is 1.78/10,000 person/years, all figures referring to the population over 55 years of age.

Key words: *Osteitis deformans, Prevalence, Incidence.*

Introduction

Paget's disease of bone (PD), also called "osteitis deformans", is a focussed disorder of bone remodelling, of unknown etiology, which occurs usually in an asymptomatic form. It is characterised by an increase in bone resorption followed by an increase in formation which gives rise to bone which is disorganised, with anomalous characteristics and altered biomechanical properties. All this drives the appearance of enlarged bone, deformed and fragile, which is the cause of its clinical manifestations and orthopaedic and neurological complications. It is imaging techniques, which to the greatest extent, allow the diagnosis of the disease. Biochemical markers for remodelled bone and gammagraphic studies are the complementary investigations which serve to assess the activity and extent of the disease. At present biphosphonates are the medical treatment of choice. The indication for treatment with antiresorptive drugs should be individualised, taking into account metabolic activity, age, the location of the disease and presence of complications[1].

PD is the most frequent bone metabolic disease in the countries of our region, after osteoporosis. Its prevalence and incidence show great variability in relation to geographic location, age, gender and race. In general, it affects adults, being infrequent in those below 40 years of age. The distribution by gender is similar predominantly in men. Its racial distribution is heterogeneous, it being non-prevalent in the native black population of Africa, Japan and South-east Asia. PD predominates in the Caucasian Anglo-Saxon race[2].

The epidemiology of PD in Spain has not been well characterised until recently by Guañabens N et al[3], who estimate it at at least 1% in those older than 55 years. This data concurs with previous data which estimates it at around 0.9-1.3%[4], with a focus of higher prevalence in Sierra Cabrera (Madrid)[5] and in Vitigudino (Salamanca)[6]. The objective of this study is to approximate the prevalence and incidence of PD in an area of the city of Barcelona (Barceloneta).

Patients and Methods

The study was carried out in 1998 in an area of the city of Barcelona (Barceloneta, Spain), in which the health care of the population is provided, almost completely through the primary care centre (CAP Barceloneta) and the University Hospital (Hospital Universitario del Mar), which is the hospital for referrals from the area. The population of the area is, according to the census of 1996, 18,509. 97% are of Caucasian origin, the remaining 3% being made up largely of people from the Magreb. The age distribution is the following: 9.9% (0-14 years), 63.8% (15-64 years) and 26.2% (> 65 years), of which 6,984 patients are over 55 years of age (2,816 men and 4,168 women).

80% have an open and active clinical history at the University Hospital (Hospital Universitario del Mar) and/or at the CAP (Centro de Asistencia Primaria) Barceloneta.

The University Hospital and the CAP Barceloneta have available digitized archives of diagnosis, treatment and complementary investigations. The search for probable cases of PD was carried out by means of a review of the digitised archives of: clinical diagnoses (CAP Barceloneta, and the Rheumatology Service and general archive of the University Hospital), anti-Paget treatments, anatomical-pathological diagnoses (the archive of the Anatomy Pathology Service of the University Hospital), diagnoses of the Nuclear Medicine Service of the University Hospital, and clinical analyses. A case was considered to be probable when the total values of alkaline phosphatase in the blood were higher than 300 UI in patients older than 55 years, and with normal liver tests (AST, ALT, GGT and bilirubin). When a probable case was identified the diagnosis of PD was confirmed through a review of their clinical history by the researchers trained in the diagnosis of PD (JB and ME). Following the confirmation of diagnosis a form was completed to gather data including: age and gender, monostotic/polyostotic form, year of diagnosis and possible complications.

Results

A total of 16 patients were identified (6 men and 10 women). The average age: 79.2 (range 65-92). The distribution according to age and gender is shown in Figure 1. What stands out is that not one case was found in anyone younger than 65 years old, and that prevalence increases with age. Also, the distribution by gender only showed a clear predominance of the female sex in the group older than 85 years. The apparent prevalence in the population studied > 55 years old was 0.23%. The symptomatic cases registered were 9 (9/16), which represents 56%. Kanis JA[7] says that only 20% of patients with PD show any clinical manifestation. Following from this premise it could be inferred that the total number of symptomatic patients in our population is 45, with a prevalence calculated at 0.64%. The polyostotic (8) and monostotic (8) forms are present with the same frequency.

In the period 1996–2000 5 new case of PD were diagnosed in patients older than 55 years, giving an apparent incidence of 1.78/10,000 person/years.

A difficulty with the study is that in assessing prevalence in a predominantly asymptomatic disease there is a dissociation between detected cases and real cases. Detected cases allow us to define the apparent prevalence and the real cases (symptomatic detected + non-detected cases) as the real prevalence.

Discussion

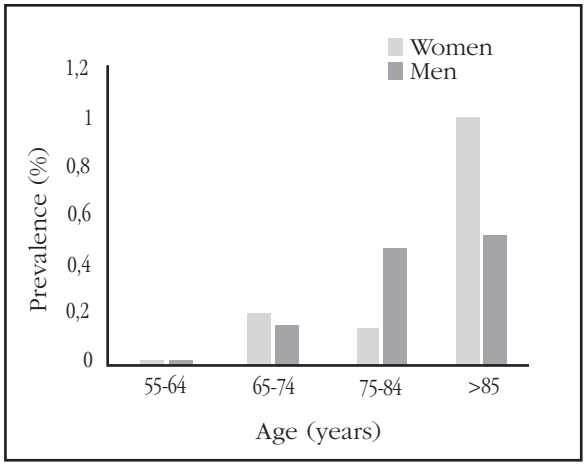
The importance of epidemiological studies of PD reside in the fact that they permit the establishment of a hypothesis on the etiology and pathology of the disease, thus providing social/public health data which could help managers in the assignment of resources in an efficient way.

In 1932 in Germany, Schmorl[8] was the first to calculate the prevalence of the disease by carrying out 4,614 autopsies on people who had died aged 40 or more years, establishing a prevalence of 3%. In England, Collins DH[9], in 650 autopsies, found a prevalence of 3.7%. Pygott F[10] in 1957 determined, through a radiological review of the pelvis and lumbar spinal column, a prevalence of 3-4% in Great Britain.

Detheridge FM et al[4], evaluated the prevalence in western Europe through a postal questionnaire carried out with radiographers in 13 cities in 9 European countries. Confirming the high prevalence of this disease in Great Britain, at around 5-6%, much the same as the findings of the Barker DJ et al[11,12]. These authors evaluated the radiological prevalence of PD in 14 cities of Great Britain, the study widening 3 years later with the inclusion of 31. The result of both studies show an average prevalence of 5%, being higher in the cities of the north east (focussed on Lancashire) where it varies between 6 and 8%. In a recent study van Staa TP et al[13] found, through the review of the centralised diagnostic archives (General Practice Research Database) of England and Wales, a prevalence for clinical PD of 0.3% in the population over 55 years old. The incidence found at 75 years, was 5/10,000 patient/years in males and 3/10,000 patient/years in females, with a decline in incidence in the last 11 years. Studies carried out in France, with a similar methodology, show a prevalence of 1.5-2.5%[14]. In a recent study, Lecuyer et al[15], through a review of radiographies of dorsal and lumbar spinal column carried out in the course of an epidemiological study of osteoporosis (EPIDOS), found a prevalence in women over 75 year of between 1.1 and 1.8%. In the Netherlands Eekhoff M et al[16], using the results of the Rotterdam Study of the incidence and risk factors of various chronic diseases, identified cases of PD in this population by studying those subjects who had high levels of total alkaline phosphotase in the blood (higher than 2 DE on average) and the presence of radiographic signs of PD. The prevalence was estimated at 3.6%. In the rest of the European countries the prevalence is lower: Sweden (Malmo) 0.4; Italy (Palermo) 0.5%; Greece (Athens) 0.5%. In Spain an intermediate prevalence is observed, 1.3% in Valencia and 0.9% in La Coruña, similar to that of Portugal (Oporto 0.9%), Italy (Milan 1%) or Germany (Essen 1.3%)[4]. The rarity of this disease in the Nordic countries has also been confirmed in other studies carried out in Norway and Finland[17]. In Ireland the prevalence was 1.7% in Dublin, less than might be expected in a country which neighbours Great Britain. However, the prevalence of 0.7% found in Galway, in the north west of Ireland is comparable with the rest of Europe[18].

The prevalence in the United States is estimated at around 1-2% in the general population, with no differences in gender, or ethnic group, except in Native Americans, in whom it is very low. The prevalence of 3% in New York compared to 1% in Atlanta, shows a pronounced variation in the distribution of this disease between the cities of the north and the south of the country[19,20].

Figure 1: Prevalence of Paget's disease of bone, according to age and gender



The few epidemiological studies carried out on the non-Caucasian population of Africa reveal prevalences of between 1.3 and 2.4% in those over 55 years old[21].

Countries with predominantly Anglo-Saxon immigration, such as Australia or New Zealand, show a high level of prevalence. It has been suggested that this could be attributed to emigration from Great Britain. The prevalence in British immigrants to Australia is 4%, intermediate between the 5% for Britons who have stayed in Great Britain, and the 3.2% for native Australians with British origins[22].

In summary the prevalence varies between the 5% seen in the population of people over 50 years old in Great Britain and the 0.4-1.3% seen in the other countries of Europe, with New Zealand, the United States and Australia being similar to that of Europe. In countries such as the Scandinavian nations, Japan, China and the Middle East PD is rare.

The heterogeneous geographical distribution of this disease, as has been commented on, is well known, as is the existence of areas of very high prevalence, "hot spots" which have motivated the study of possible etiopathogenic factors. In the "hot spot" of Lancashire, Great Britain, with a prevalence of 6.3 – 8.3% in those over 55 years of age, the existence of any exclusive climatic or geological characteristics which could give some inkling of an explanation of the etiology of PD[11], has not been found. In the "hot spot" of the Sierra de Cabrera, in Madrid (Spain), with a prevalence of 6.37% in those over 40 years of age, a probable genetic conditioning has been postulated, through the detection of a group of 6 families with 15 members affected by the disease[5]. In Vitigudino, Salamanca (Spain), the prevalence is

Table 1: Description of the principal characteristics of the most relevant studies on the prevalence of Paget's disease of bone

Authors and bibliografical reference	Year	Location	Methodology	Prevalence (%)
Gardner MJ et al[21]	1978	Australia	Abdominal X-ray review, barium study and endovenous urography	3.2-4
Barker DJ et al[10]	1980	Great Britain	Abdominal X-ray review	5
Barker DJ et al[9]	1980	Great Britain (Lancashire)	Abdominal X-ray review	6.3-8.3
Guyer PB et al[8]	1980	USA	Abdominal X-ray review	1-3
Detheridge FM et al[3]	1982	Europe	Postal survey and abdominal X-ray review	0.4-4.6
Detheridge FM et al[17]	1983	Ireland	Postal survey	0.7-1.7
Morales-Piga A et al[4]	1990	Spain (Madrid)	Determination of total alkaline phosphatases and radiological confirmation	6.3
Renier JC et al[13]	1995	France (Anjou)	Endovenous urography review	1.8
Miron-Canelo JA[5]	1997	Spain (Salamanca)	Questionnaire, radiological study and determination of total alkaline phosphatases and radiological confirmation	5.7
Altman RD et al[19]	2000	USA	Pelvic X-ray review.	1-2
van Staa TP et al[12]	2004	England and Wales	Review of diagnoses from populational database (General Practice Research Database)	0.3 *
Eekhoff M et al[15]	2004	Netherlands (Rotterdam)	Determination of total alkaline phosphatases and radiological confirmation	3.6
Guañabens N et al[3]	2008	Spain	Abdominal X-ray review	1,0

* Clinical prevalence

5.7% in those over 40 years of age, much greater than that reported in other parts of the country, and higher than that estimated for the south of Europe[6]. Recently, new areas of high prevalence have been described in Spain[23]. Table 1 describes the characteristics of the principal studies of prevalence.

The polyostotic form of the disease is more common than the monostotic form, as has been shown in a range of studies. Monfort et al[24], through an evaluation of 250 patients, found that 73% had the poliostotic from.

Recent studies seem to indicate "secular" changes concerning the age of presentation, the severity of the disease (evaluated by the extent of the affectation of the bone and/or levels of alkaline phosphates in the blood), predominance of one gender or other, and geographic location. The data for prevalence, standardised by age and gender, of Cooper et al[25] in great Britain, indicate a reduction in prevalence from 5% in 1974, to 2%, twenty years later, this decrease being more marked in certain zones, such as Lancashire, considered "hot spots" of high prevalence. In the United States a similar phenomenon has been described[26]. The majority of the studies confirm that the age of presentation continues to get higher. Cundy et al[27], show that at the beginning of the 70s the average age of presentation was 62 years, lower than that of 71 years of the last decade. The number of certificates of disability due to PD or its complications has diminished in the last 30 years, in the same way as the disease, which suggests a tendency to less sever forms[28-31].

The results obtained in this study in Barceloneta, a district of the city of Barcelona, show that the real prevalence calculated for this area is in the region of 0.6-0.7%. In Europe, with the exception of Great Britain, it varies between 0.4 and 1.3%[4]. The prevalence found is lower than

that found in two Spanish cities – Valencia, 1.3% and La Coruña, 0.9 – by Detheridge FM et a[4]. In respect of this last work, what stands out is that the results are the product of a postal questionnaire carried out in radiological services in diverse cities of Europe with the limitations that this methodology can bring.

We do not know of the existence of other studies carried out using the same methodology, at present, in Spain. The results obtained, very probably, approximate to the reality of the prevalence in our locality, an area in which health care is provided almost exclusively by the Primary Care Centre and by the referent hospital, and having had systemic access to the digitized registers of diagnosis and complementary investigations which makes it probable that non-diagnosed cases are scarce. Differently from other studies, in which one might question the certainty of the diagnosis of PD, the cases were confirmed through an exhaustive review of the clinical history. The population studied does not differ much in its distribution by age, gender and ethnicity, from that of the Spanish population, which allows the extrapolation of the results to the rest of the country, except that the average age is somewhat higher than the average for the Spanish population as a whole, and that this study was carried out in an urban area. To which can be added the fact that it was carried out in a mixture of the hospital and extra-hospital population.

In conclusion, the prevalence of PD in the area of Barceloneta (Barcelona, Spain), is similar to the average prevalence in Europe, and very close to that in other parts of Spain, despite the non-existence of truly representative studies of the global impact of this disease in our country. We would support any study which might answer the epidemiological questions raised by this interesting and complex illness.

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Study of bone mass in the alcoholic patient

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Summary
A prospective descriptive study was conducted to assess the alteration in bone mineral density (BMD) in alcoholic patients, under the age of 65 and free of non-modifiable risk factors for osteoporosis, who were admitted to the Clinical Toxicology Unit for detoxification and subsequent supervision, between January 2007 and May 2008. Nutritional profile and liver function were also analysed in order to establish a relationship with the BMD observed in subsequent studies. 36 male patients were studied with an average age of 51 years. Pathological levels of bone mass (in the spinal column and hip) were detected in 53% of patients (42% with osteopenia and 11% with osteoporosis), a much higher percentage than that expected in a male population of such an age. Vertebral fractures were observed in six patients (16%) and hip fractures in four (11%).
The care of alcoholic patients must be comprehensive and depends on the state of the addictive disorder, with the active treatment of the alcoholism being essential and a priority. However, given the risk of fractures associated with falls, once a metabolic abnormality is diagnosed, the appropriate treatment should be initiated as soon as possible.

Key words: *Osteoporosis, Osteopenia, Alcoholism.*

Introduction
Osteoporosis (OP) is a systemic disease of the skeleton characterised by compromised bone resistance, which predisposed an increased risk of fracture[1]. Bone resistance is related to two properties of the bone: the bone mineral density (quantity) and its quality.

Bone mineral density (BMD) is expressed in grams of mineral by surface or volume and can be estimated using different techniques, although double energy axial radiological absorptionometry (DEXA) is considered the standard reference for this purpose. Bone quality refers to the macro- and micro-architecture, accumulated microlesions, mineralisation and remodelling of the bone.

In 1994, the OMS[2] established some densitometric criteria which categorised the situations in which it is possible to measure the bone density using DEXA, and related this to the value of the peak bone mass (T-score). As much for carrying out densitometries (it is not viable to screen the whole of the population), as for the initiation of treatments, it is essential to evaluate the risk factors, which we obtain from epidemiological studies in which we confirm which factors coincide in more patients[3] (Table 1).

Since 2008 we have had available a tool, based on the work of Kanis 2005[4], which allows us to calculate the index of fracture. This is the FRAX Index, available on the internet (www.shef.ac.uk/FRAX/), which calculates the risk of fracture at 10 years, both vertebral and non-vertebral, and hip, fractures, assessing risk factors and BMD of the femoral neck. This can be calculated without the densitometric value, so allowing the establishment of a patient's treatment without being dependent on densitometry results. Among the risk factors included is alcohol intake, which

makes this approach more useful for the patients discussed here.

In Spain OP affects around 2 million women over 50 years of age and some 750,000 males[5]. However, it is an illness which is underestimated by the patients themselves, by the authorities, and by health professionals[6].

The excessive consumption of alcohol is an important risk factor for osteoporosis, above all in the male population, and is included, as we have just seen, in the FRAX Index. The consumption of alcohol reduces bone mass by modifying bone formation and remodelling[7-10]. In adolescence it reduces the peak bone mass, which increases the probability of osteopenia or osteoporosis in adulthood. A high intake of alcohol is associated with pathological and dietetic changes which can have a negative impact on bone metabolism causing osteoporosis, such as: malnutrition, vitamin D deficiency and parathormone (PTH), hypoproteinemia, hepatopathia, hypomagesemia, deficiency in Group B vitamins and folic acid, excess of iron, diminution f testosterone[11-14]. Other factors, such as a reduction in B12 and folates[15], or hyperhomocisteinemia[16], might also have a negative impact, although their importance is yet to be determined. These chronic changes will cause a loss of bone mass which will result in osteopenia and osteoporosis at a much earlier age[17-21].

In men, OP usually happens unseen, due to its scarce clinical symptoms and the deterioration which accompanies alcoholic patients at many psycho-organic levels (hepatopathies, neuropathies, etc). If fractures occur (and the frequent falls experienced by alcoholic patients increase their incidence) the suspicion of OP is more evident and facilitates the diagnosis.

The principal objective of our study was to asses the change in bone mass in male patients with alcohol dependency (according to the DSM-IV criteria)[22].

The secondary objectives were to assess the analytical study of phosphocalcic metabolism , the existence of bone fractures through anamnesis of the patient (extravertebral fractures) and radiological study of the dorso-lumbar spinal column profile (vertebral fractures). We also assess the deficiency of magnesium, proteins and vitamins in group B, hormonal changes (thyroid function and PTH), excess of iron and study of liver function.

Material and Methods

The study involved patients who had attended the Unidad de Toxicología Clínica from January 2007 t o May 2008, admitted for detoxification, followed by treatment to combat alcohol dependency, who were less than 65 years old and had extensive other non-modifiable risk factors for osteoporosis, who had been informed about the study, and who gave their informed consent.

We present a descriptive prospective study which brings together a total of 36 patients who meet the criteria listed.

On the patients selected a detailed anamnesis of their history of alcoholism (duration of the dependence, type of consumption, episodic or continuous, quantity of alcohol, maximum period of abstention), personal medical, psychiatric and bone fracture history, and body mass index (BMI), was carried out.

A standard analysis was carried out on all patients, which studied liver function, markers for hepatitis B & C & Mantoux viruses, also adding the factors to be assessed in our study calcium and phosphorus in blood and urine at 24 hours, PTH, vitamin D, osteocalcine, tartrate-resistant acid phosphatase (FATr), bone alkaline phosphatase, C-terminal telopeptide (CTX), magnesium, vitamin B12 and folic acid.

In addition to a radiological study of the thorax and abdominal echography, we also carried out a radiological study of the dorso-lumbar spinal column in profile, to detect fractures, which we took as the reduction of its anterior, middle and posterior height, above 20% (Genant index), as well as densitometry of the spinal column and hip, by means of double photon absorptiometry (Lunar).

The data were analysed statistically with the SPSS programme, version 15.

Results

36 male patients with an average age of 51 years were included in the study. The average body mass index was 25. The patients had an average duration of alcohol dependency of 26 years, with a continuous pattern of consumption in the majority of cases (72%) and an average daily consumption of 21 standard units of drink (UBE), with periods of abstinence of a maximum of 9 months.

30% of patients had psychiatric histories, most of which were anxiety-depressive disorder (25%). In terms of known medical history, predominant in order of frequency were: alcoholic hepatitis 47% (cirrosis 19.5%), ulcer 39%, diabetes 16%, pancreatitis 13%, polyneuropathia 11% and encephalopathia 11%. 94% of patients combined tobacco smoking with their drinking habit, and 6% consumed other drugs.

Liver affectation, as might be expected, is common, with the echographic study finding hepatic steatosis (enlargement and echogenicity) in 25% of patients and signs of portal hypertension in 44%. 42% of patients had altered coagulation, with Quick's diminution in 42% of patients. GOT was high in 36% of cases, with an average of 79 U/L (normal interval 10-35 U/L), GPT was high in 58% of patients, with an average of 58U/L (10-45 U/L), FA was normal in 92% of cases, GGT high in 94%, with 365 U/L as the average (8-55 U/L). Bilirubin was high in 42%, and amylase and lipase normal in 19%.

In terms of indices of nutritional profile, the following findings stand out: anemia in 50% of patients, macrocytosis in 47%, B12 deficiency in 14%, reduction in folic acid in 23% and of magnesium in 51%. 12% of patients had hypoalbuminemia. Ferritin was high in 48% of cases. Study of lipids: hypocholesterolemia in 12% and hypoglyc-

Table 1. Risk factors for osteoporotic fractures. SEIOMM Guides 2008[3]

	High risk	Moderate risk
Mixed factors (BMD + independent component)	- Advanced age - Previous personal history of osteoporotic fractures - Maternal history of femoral fracture - Low body weight* - Glucocorticoids** - High bone turnover	- Diabetes mellitus - Tobacco smoking
Associated with low BDM	- Hypogonadism in males - Primary hyperparathyroidism - Anorexia nervosa - Prolonged immobility - Anticonvulsants - Malabsorption syndrome	- Female sex - Early menopause*** - Primary and secondary amenorrea - Rheumatoid arthritis - Hyperthyroidism - Vitamin D deficiency - Low calcium intake****

High risk: when relative risk > 2
Moderate risk: relative risk > 1 and < 2
* Body mass index < 20kg/M^2
** Period greater than 3 months and more than 7.5 mg prednisone/day
*** Before 45 years of age
**** Lower than 500-800 mg/day
Factors related to the tendency to having falls and associated with the production of fractures, are considered independent factors. BMD: Bone Mineral Density

eridemia in 14%; hypercholesterolemia in 36% and hyperglyceridemia in 17%.

Bone metabolism study: no changes in values of calcium or phosphorus were detected. PTH was high in 5% of cases, with values 10% higher than normal in these cases. Osteocalcine and bone fraction of alkaline phosphatases were normal. FATr was high in 50% of cases (18 patients). CTX was increased in 36.1% of cases (13 patients).

According to the OMS' densitometric criteria, fifteen patients had osteopenia (41.6%) and four, osteoporosis (11.1%). Of the fifteen patients with osteopenia, in seven it was present in the spinal column and hip, in four only in the spinal column and in four only in the hip. Of the four patients with osteoporosis, in three cases this was detected in the spinal column and in one case, in the hip. The three patients with densitometric osteoporosis in the spinal column had osteopenia in the hip, and the case of osteoporosis in the hip had osteopenia in the spinal column.

We found vertebral fractures in 6 patients (16.6%) and hip fractures in 4 patients (11.1%). We did not find other extravertebral fractures. The existence of costal fractures, so prevalent in alcoholic patients, was not evaluated, since they frequently pass unnoticed clinically and radiologically, we would have required other complementary investigations (gammagraphy) to identify them with certainty.

Discussion

We have studied a group of patients with a history of severe alcoholism and secondary, alcohol related, organic damage in the main hepatopathy (69% steatosis and 44% portal hypertension) and ulcers. A high percentage presented with nutritional deficiencies: anemia, hypoalbuminemia and vitamin deficiencies. These were accompanied by active tobacco smoking in most of the patients (94%). Only 6% had an addiction to other drugs.

Pathological levels of bone mass were detected in 53% of patients (42% osteopenia and 11% osteoporosis), a percentage much higher than would be expected in a population of males of the same age[23,24]. This increase in oseopenia/osteoporosis concurs with that described in other studies of alcoholic patients[25].

In the parameters related to bone metabolism, we only detected an increase in the markers for bone resorption, both in FATr (50%) and CTX (13%), as a manifestation of an increase in bone resorption in these patients. PTH was high in 2 patients (5.5% of cases), with a minimum deviation from normal.

We detected vertebral fractures in 6 patients (16.6%) and of the hip in 4 patients (11.1%). Four patients with vertebral fractures had osteopenia in the spinal column and hip and two of those had osteoporosis in the spinal column. Of the four patients with hip fractures, one had osteo-

porosis in the hip (the only case), while the three remaining had osteopenia in the hip. We only considered fractures considered to be osteoporotic, that is, produced by low impact trauma or without known cause, discarding those caused by significant trauma. Other extravertebral fractures were not found and costal fractures were not studied.

The care of alcoholic patients needs to be comprehensive and we must study the impact of alcohol on the different organs and systems, whether the patient is admitted for detoxification, or due to alcohol-related secondary pathologies. The nature of this integrated approach will depend on the state of their addictive pathology, with the active treatment of the alcoholism being essential. However, given the importance of fractures associated with osteoporosis in the alcoholic patient, which diminishes their quality of life and increases mortality, above all through fracture of the hip, we believe it essential to assess the use of antifracture treatment in these patients. The application of the FRAX index could help us in this, since it already includes alcohol as a risk factor, and could help us take decisions in light of a prediction of a fracture in the next 10 years.

In treating patients with digestive intolerances, and possibly with little adherence to treatment, the current availability of new drugs such as zoledronic acid, which can be given intravenously and with an annual dose, could contribute to a reduction in fractures in these patients, as well as reducing their mortality, which is increased by fractures[26,27]. Since they are often in poor health, we must ensure that these patients do not have a septic mouth, to reduce the possibility of mandibular osteonecrosis[28].

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Bone mineral metabolism in inflammatory bowel disease

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Summary
Ulcerous colitis and Crohn's disease constitute the principal components of inflammatory bowel disease (IBD). Osteoporosis is a well-known complication of IBD presenting a multifactorial etiology, although the importance of the inflammatory process in itself seems to be ever greater. The end of this article reviews the existing data on bone mineral metabolism in these patients, both in relation to the prevalence of the loss of bone mass, as in the situation of the markers for bone turnover, the factors involved, as well as the risk factors. In this way, it is intended to shine a light on the importance of osteoporosis in IBD.

Key words: *Ulcerous colitis, Crohn's disease, Inflammatory bowel disease, Bone mineral metabolism.*

Introduction
Inflammatory bowel disease (IBD) is fundamentally comprised of two processes: ulcerous colitis (UC) and Crohn's disease (CD). Although tending to be considered in a combined form, the pathogeny of the disorders is not yet known, each possessing distinct clinical characteristics and histologies. The objective of this work is to carry out a review of the literature on the current knowledge with respect to bone mineral metabolism in patients with IBD.

UC consists of a non-transmural and recurrent inflammatory process which is limited to the colon, and which can manifest itself as proctitis, left-sided colitis, or pancolitis. Typical patients present with bloody diarrhoea (often at night and after meals), accompanied by pus, mucus or both, along with a colic-type abdominal pain, the more infrequent serious symptoms being left-sided colitis and proctitis. The diagnosis is clinical and is confirmed by means of endoscopies and histology.

CD is an inflammatory process, transmural and recurring, of the gastrointestinal mucosa, which can affect any part of the digestive tract, from the mouth to the anus. Typical presentations include segmentary affectation of the gastrointestinal tract, with healthy areas of intestine among affected segments, as well as the development of evolving complications among which are included fistulas, abscesses and stenosis. Its diagnosis is based on the combination of clinical data, analysis, X-rays, endoscopies and anatomopathologies[1].

Osteoporosis is a well-known complication of IBD in general. The presence of bone demineralisation and osteoporosis in IBD was reported for the first time by Genant et al in 1976[2]. Transversal studies calculated the prevalence of low bone mass at 30% of patients. In general, the average BMD would be 10% less than in the general population[3], but, since they are distinct entities, it seems reasonable to make a differential evaluation.

Bone mineral density in IBD

There are numerous studies which have permitted the documentation of the presence of loss of bone which varies between 18% and 42% (Table 1)[3-12]. The wide variation in the results obtained in these studies could be influenced by diverse factors, the method and the part of the skeleton where the measurements are carried out, and the selection of the patients, among others. However, these data have clearly shown that those patients with IBD have lower bone mass when compared with a population of healthy controls[7,13-15].

The loss of bone seems to be more acute in CD than in UC. A transversal study found a reduction of 7.3% in average BMD in patients with Crohn's disease in relation to those with UC and with healthy subjects[13]. Another found a prevalence of osteoporosis in CD of 59% against 43% in UC[16]. However, in the study by Adizzone S et al, despite finding a prevalence of osteopenia of 55% and of osteoporosis of 37% in CD, against 67% of osteopenia and 18% of osteoporosis respectively in UC, the differences were not statistically significant[17]. The same happens in other studies[3,10,18-21]; there is another group that has reported the contrary[21]. On the other hand, although women and men become affected equally, the change can become more serious in males; what's more, although it has not been possible to establish a relationship between the intensity of the loss of bone mass and the duration of the disease, jejunal affectation and ileal resection can bring greater risk[22].

Markers for bone turnover in IBD

The existing studies in relation to levels of markers for bone turnover and IBD, both in formation and in resorption, have not brought conclusive results on whether or not they found changes with respect to the healthy population. This confusion is due in part to the heterogeneity of the studies, many of which were transversal, with some patients in an active phase and others inactive, not always comparing with healthy controls, and under different treatments, such as glucocorticosteroids (GC) or immunosuppressors, which can have a greater influence over the bone mineral markers than that caused by the disease itself. What's more, there is no uniformity in the markers for formation and measured bone turnover.

The study by Gilman et al, with 47 patients with CD, 25 with UC and their respective healthy controls, found a significant increase in bone alkaline phosphatase (BALP) in the blood, and amino-terminal telopetide of collagen type 1 (NTX) in the urine, in IBD patients compared with healthy controls, while the levels of osteocalcine (OC) was found to be significantly diminished[23]. Another study by Pollack et al, found in 63 patients with CD and 41 with UC, low levels of OC in 7% of those patients, while those levels of NTX were found to have risen in 25% of patients[24]. Another group found, in a total of 72 patients with IBD, a decrease in levels of OC and an increase in levels of NTX – the latter negatively correlated with bone mass in the lumbar spinal column and femoral neck[25]. Arizzone et al found a significant increase in levels of OC and of carboxy-terminal telopetide of collagen type 1 (CTX) in the 40 patients with UC they evaluated, but not in those 51 with CD[17]. On a different tack, in a study only of patients with Crohn's disease, Robinson et al only found elevated levels of urinary deoxipiridoline (DPD) in comparison with 28 healthy controls, but found no differences in levels of OC and CTX[26]. Neither were differences found in levels of OC in 150 patients with IBD compared with 73 healthy controls, although they did find higher levels of CTX. In addition, in this same study, both patients with CD and with UC who were found to be active showed levels of OC and CTX higher than those were not. In the case of patients with UC, the levels of CTX were found to be higher in those affected by pancolitis as opposed to those who only had left-sided colitis[27]. On the other hand, Miheller et al, in a study of 23 patients with UC, 26 with CD and 46 healthy controls, found a significant elevation in levels of CTX in both groups with respect to the controls[28]. In a wider study with 258 patients, only with CD, the levels of urinary DPD and BALP in the blood were found to be in the normal range and there were no difference between those presenting with osteoporosis and those who did not; in terms of the levels of NTX, although these were normal they were significantly higher in those with osteoporosis[29].

Finally, although the impact of changes in the markers for bone turnover in IBC on the risk of fracture has not been studied, there is evidence that the increased levels of markers for bone resorption in IBD is associated with the loss of bone mass. Thus, Pollack et al, using an analysis by quartiles, show that the patients with IBD who present with highest urinary concentrations of NTX show a greater loss of bone mass in the lumbar spinal column in comparison with those presenting with lower levels in the urine. The raising of the levels of markers for bone resorption is recognised as a risk factor for fractures, at least in menopausal women[16,30]

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Risk of fracture in IBD

The consequence of osteoporosis is the development of fractures. However, the increase in the risk of fractures in IBD with respect to the general population is not well established. Klaus et al, in a study developed in Germany, found a high prevalence (22%) of osteoporotic vertebral fractures in 156 patients with CD and Z-score < -1, including in patients younger than 30 years old[31]. In a cohort of 6027 patients in Canada, compared with 60270 controls, Bernstein et al found an increased total risk of fracture of 47%, being higher for vertebral fractures (54%), with no difference between women and men, nor between CD and UC; there was indeed an increased risk of fracture in males with UC in comparison with the women[32]. On the other hand, Vestergaard et al

Table 1. Prevalence of osteopenia and osteoporosis in IBD

	Population	T-score/ Z-score	Prevalence Osteopenia	Prevalence Osteoporosis
Abitbol et al	CD and UC	Z-score	43%	13,09%
Bjarnasson et al	CD and UC	T-score	78%	29%
Clements et al	CD, others	Z-score	-	30,7%
Compston et al	CD and UC	Z-score	-	30,6%
Gokhale et al	CD and UC	Z-score	-	7%
Martínez et al	CD and UC	-	49,3%	27,4%
Pigot et al	CD and UC	Z-score	-	23%
Pollak et al	CD and UC	T-score	34%	42%
Schoon et al	CD and UC	Z-score	1,5%	26%
Schulte et al	CD and UC	Z-score	-	11%
Siffledeen et al	CD	-	51%	13%
Silvennoinen et al	CD and UC	Z-score	-	5,9%
Sinnot et al	CD	Z-score	-	27%
Staun et al	CD	Z-score	-	20%

found an increased total risk of fracture in women with CD (RR 2.5), but not in males (RR 0.6), nor in patients with UC (RR 1.1), out of a total of 383 patients with Crohn's, 434 with UC and 635 controls in Denmark[33]. Although there are discrepancies in this respect. For example, Loftus et al did not detect an increase in the incidence of fractures in a total of 238 patients with CD in the USA, with respect to the control population, with an RR near to 1 in all their findings[34].

In general it is accepted that the increased risk of fracture is modest, and comparable between patients with CD and UC. For all types of fracture the relative risk for CD is 1.3 and 1.2 for UC, being somewhat higher in the case of hip fractures (1.5 for CD and 1.4 for UC). Since the majority of studies are based on reports of fractures it is possible that the prevalence of vertebral fractures (and of fractures in general) might be underestimated. In fact the only studies which have used X-ray quantitative morphometry of the spinal column found a very high prevalence of vertebral fractures (14-25%)[35,36]. Also found were various risk factors for osteoporotic fractures in IBD, such as low BMD, age, use of GC and the activity of the patient. BMD, in turn can be seen as a negative influence on for women at a young age when diagnosed, for the male sex, low body mass index (BMI), duration of the disease, the previous presence of Ileal resection, accumulated dose of GC, reduced physical activity and smoking[35]. It is important to underline the fact that not all fractures (especially vertebral) are symptomatic and/or vertebral deformities, whose risk is also higher among the population with IBD[31], and whose presence can be used to identify patients with highest risk of fractures so as to focus prevention.

Pathogenesis of osteoporosis in IBD

The etiology of osteoporosis in IBD is multifactorial (Table 2). The factors which can influence its development can be divided into: a) factors common to those of the rest of the population (low weight, family antecedence, age, female sex, menopause, tobacco,…) and; b) specific factors such as genetic influence, deficiency in vitamins D and K, treatment with GC, hormonal changes and the inflammatory process in itself[29,33,37,38].

Genetic factors

There are a number of genes which influence the functioning of the osteoblasts, and it is possible that protein 5 related to the receptor LDL (LRP5) is one of these. Thus, a range of findings have shown that mutations of the gene LRP5, which results in a loss of functionality, gives rise to bone defects similar to those seen in the syndrome osteoporosis-pseudoglioma, supporting the fundamental role of this gene in the integrity of the skeleton. A range of polymorphisms have been described (such as rs491347, rs 1784235, and A1330 V) which are associated with a greater susceptibility to the development of osteoporosis and fractures in humans, supporting therefore the possible role of gene LRP5 in the acquisition of peak bone mass.

Table 2. Principal risk factors for osteoporosis in IBD

- Advanced age
- Taking corticoids
- Malnutrition
- Low body mass index
- Poor absorption of vitamin D, calcium and vitamin K
- Immobilisation
- Antecedence of fragility-related fracture
- Hypogonadism
- Tobacco smoking
- Chronic inflammation

One the other hand, the identification of receptors for vitamin D (VDR) in peripheric mononuclear blood cells has boosted an interest in this vitamin as a possible regulator of the immune system. Vitamin D deficit has been related to a range of diseases, among which is osteoporosis mediated by an immune mechanism, as that which appears to occur in IBD. There are various polymorphisms of the gene for VDR associated with the development of osteoporosis which have been studied, above all Bsm I.

Another important candidate for the genetic susceptibility for osteoporosis is the gene coded as TGβ-1. Various polymorphisms of this gene have been identified, and a number of works suggest that certain allelic variants of TGβ-1 could regulate BMD and susceptibility to osteoporotic fracture.

The list of genes studied is very extensive, such as, for example CYP17 (17-hydroxilase), CYPB1 (cytochrome P450), DBP (binding protein for vitamin D), GH1 (growth hormone 1), GnRH (gonadotropine-releasing hormone), IGF-II (growth factor similar to insulin type II), among many others. However, the relationship of these genes to inflammation, as a possible mechanism for osteoporosis in IBD, is not yet completely clear, but could perform a modulating role in the susceptibility to the development of a metabolic osteopathy in these patients[38].

Vitamin D deficiency

A study carried out by Driscoll Jr et al with 82 patients with CD, saw that up to 65% of them presented with low levels of 25-hydroxy-vitamin D ($25OHD_3$), and 25 of them had a deficiency (<10 ng/ml). The levels were less if there had been a previous resection of the ileum. A bone biopsy was carried out in 9 patients, with 6 of them showing osteomalacia and 3 osteoporosis[11]. More recently a study with 242 Crohn's patients found that 8% of them showed levels of $25OHD_3$ lower than 25 nmol/L, and in 22% levels lower than 40 nmol/L. However, while no differences were detected in relation to BMD in those presenting with normal levels of $25OHD_3$, there was indeed biochemical evidence of metabolic bone disease[39]. Jahnsen et al found levels of $25OHD_3$ lower than 30 nmol/L in 27% of 60 patients with CD and in 15% of 60 patients with UC, the patients with Crohn's showing concentrations significantly lower than those with UC. The levels of $25OHD_3$, however, were not related to BMD in any of the findings from skeletal measurements[40]. In the study of Gilman et al, the patients with CD showed levels of $25OHD_3$ significantly lower in comparison with the healthy controls, with 19% being lower than 40 nmol/L; in the case of the patients with UC, these also showed levels significantly lower in comparison with the healthy controls, there being levels of $25OHD_3$ below 40 nmol/L in 7% of patients[23]. Duggan et al and McCarthy et al, also found in patients with CD levels of $25OHD_3$ lower than those of healthy controls, with a prevalence of low levels of 7% and 18% respectively[41,42]. Other authors have also found high levels of $25OHD_3$ deficit[43,44].

The deficit in $25OHD_3$ is due in part to the low level of ingestion of milk products (which are enriched with these vitamins in many countries), but also to their poor absorption. In addition, due to the limitations which this disease brings in its serious state, exposure to the sun for these patients is often lacking (it should be noted that the exposure of the skin to light is the main source of the production of vitamin D). However, many patients with normal levels of $25OHD_3$ have osteoporosis, which needs to be explained by other causes.

Vitamin K deficiency

Vitamin K is a necessary cofactor for the carboxylation of the Gla proteins (gamma carboxyglutamate) by the osteoblasts, among which are found osteocalcine and the protein Gla of the matrix, both with a regulatory role in bone mineralization and remodelling. A range of studies have brought evidence of the relationship between a deficit status of vitamin K and bone mineralization. Various works have found vitamin K deficiency status in patients with IBD and a relationship with loss of bone mass. One of the possible causes of this state of deficit could be the taking of antibiotics, which alters the intestinal flora, responsible in good part for the daily requirements of vitamin K[23,41,44].

Treatment with glucocorticosteroids

Many patients require GC for the control of their disease. These inhibit the formation of bone, increase its resorption, reduce the absorption of calcium and increase its renal excretion.

The loss of bone mass is more frequent in patients with IBD who have received treatment with GC, above all in the initial months of treatment[45]. A study reported that the incidence of osteopenia was approximately double in patients who had received treatment with GC with respect to those who had not (52% as opposed to 28%)[18]. In general, it is accepted that BMD in patients with IBD correlates inversely with the accumulated dose over their lifetimes[3,13,18,19]. Some studies suggest, what's more, that the loss of bone mass associated with the use of GC is higher in women than in men[19], which means that it is more evident in patients with CD than with UC[13]. Notwithstanding

this, it is difficult to distinguish the degree of the contribution of the use of these drugs to the bone in comparison with the activity of the disease, since a high level of activity and a high degree of inflammation are indications for the use of steroids. Whilst prednisone, methylprednisolon and prednisolon have a systemic action and constitute one of the main factors which contribute to osteoporosis in IBD, budesonide, a corticoid which acts locally with low systemic bioavailability, is coming to be used increasingly in the treatment of IBD, due to its lack of systemic effect, including the loss of bone mass[46].

Alterations in sexual hormones

Amenorrea and hypergonadism are frequent in patients with IBD, probably as a consequence of the inhibitory effects of the inflammation and the steroid treatment on the pituitary function[47].

In men the GCs reduce concentrations of testosterone by at least a third, by inhibiting the secretion of gonadotropines, a known cause of osteoporosis[48].

Inflammatory activity of the disease

In some patients one sees low bone mass without there being any of the factors indicated. In some of these cases it even is noticed at the moment of diagnosis, without having previously received any type of treatment[49]. In addition, osteoporosis is frequent in patients with IBD who take GC in low doses and who have normal levels of vitamin D[10]. Therefore, it is thought that the disease itself could provoke a reduction in bone mass, perhaps measured by an increase in the production of citoquines in the intestine produced by the T lymphocytes and other inflammatory cells such as the macrophages, which could lead to the activation of the osteoclasts, without a compensatory increase in bone formation[10,18,49,50]. Some of these citoquines implicated could be tumor necrosis factor α (TNF-α), interleukin 6 (IL-6), interleukin 1 (IL-1) and interleukin 2 (IL-2)[50]. Within the mononuclear cells the fundamental transcription factor is nuclear factor kappa-β (NFκβ), which regulates the transcription of IL-1 and IL-6, among others, as well as regulating the expression of other pro-inflammatory genes such as TNF-α and adhesion molecules[46].

The levels of a range of osteoclast activators with pro-inflammatory activity (including IL-1, IL-6 and TNF-α) are found to be higher in IBD. There is evidence which supports the role of IL-6 in osteoporosis resulting from the loss of male and female steroids. In addition, genetic variants of IL-6 and the antagonist of the receptor of IL-1 have been identified, which are correlated with the clinical course of IBD and the degree of loss of bone mass[46]. On the other hand, it is known that the models of colitis in mice deficient in IL-2 develop colitis and osteopenia[51].

The system constituted for binding the receptor activator of NFκβ (RANKL) and osteoprotegerina (OPG) represents a potential nexus in the union between inflammation and bone homeostasis, and also an example of osteopenia brought about by inflammation, as occurs in IBD. The equilibrium between RANKL and OPG is of vital importance in osteoclastogenesis, by way of the interaction of RANK, on the surface of the osteoclasts, with its ligand RANKL inducing osteoclastogenesis, whilst OPG proceeding from the osteoblasts blocks this interaction, inhibiting the formation of osteoclasts. The pro-inflammatory citoquines induce the formation of RANKL, and the activated T lymphocytes can activated osteoclastogenesis directly through the RANKL, with the consequent loss of bone mass[38]. Recent studies suggest that the changes in equilibrium between RANKL and OPG could be responsible for the loss of bone mass in patients with IBD. Thus, plasmatic levels of OPG and RANKL correlate with BMD and the treatment for IBD[52]. In one study, it is seen that the plasmatic levels of OPG are found to be 2.4 times higher in CD and 1.9 times higher in UC. The elevated levels of OPG could represent a continual homeostatic response, an attempt to oppose the osteoclastogenesis induced by RANKL or TNF-α, and thus maintain normal bone mass[53].

In relation to the effect of the inflammatory activity of the disease on bone mass. Reffitt et al studied a cohort of 137 patients with IBD and found that their bone mass was higher the greater time they were in remission. In addition, the patients who took azatioprine and were in remission had greater bone mass[54]. In this area there are various studies which have tried to assess the possible effect of anti-TNF drugs (approved for treatment of moderate to serious cases which do not respond to conventional treatment), specifically infliximab, taken to control the inflammatory process, can have on bone metabolism.

Franchimont et al analysed the evolution of bone metabolism in 71 patients with CD treated with infliximab. Baseline markers for formation and resorption were measured and then at 8 weeks on completion the treatment (a single dose in luminal forms and 3 doses in fistular forms). An increase was seen in the markers for formation (with a median of change of 14-51% according to the marker) and a decrease in that of resorption (median of change 11%). The authors found a clinically significant increase (at least 30%) in the markers for bone formation in 30-61% of the patients (depending on the marker) and a clinically significant decrease (at least 30%) in the marker for resorption in 38% of the patients. No significant association with any of the demographic parameters nor clinical measures (including the clinical or biological response to infliximab), were found. These results, however, were not equal in all patients, in such a way that only 8.5% showed an increase in the markers for formation together with a decrease in those of resorption. The authors conclude that treatment with inflixmab produces a rapid improvement in the profile of the markers for bone turnover, independently of the clinical response to it, although the long term effects on

the risk of fracture are to be determined[57]. In the same vein, another study with 24 patients with active CD treated with a single dose of infliximab found a significant increase in markers for bone formation (BALP and OC) during the 4 months they were followed; whereas the decrease in the marker for bone resorption measured (NTX) was not statistically significant, as neither were the differences found between the responders and non-responders[55]. Abreu et al also found an association between treatment with a dose of inflximab and an increase in the marker for bone absorption (BALP) measured at four weeks, independently from the response to it or the taking of GC; no changes were found with respect to the marker for resorption (NTX)[56]. More recently a study with 103 infant patients with CD, across 54 weeks of treatment with infliximab, found an increase in markers for formation (BALP, N-terminal propeptide of collagen type 1) which was associated with an increase in lineal growth, and which the authors consider would go in favour of blocking the effects of TNF-α on the osteoblasts. Similarly, they also found an increase in markers for bone resorption (CTX, DPD) which the authors justify as reflecting the link between formation and resorption and the increase in lineal growth[57].

Bernstein et al evaluate the change in bone mass in the femoral neck and lumbar spinal column in 46 patients with CD treated with infliximab as maintenance. There was a gain in bone mineral density at all the points of measurement (2.4% in the lumbar spinal column, 2.8% in the trocanter and 2.6% in the femoral neck), which happened in spite of treatment with GC (28%). Neither was there found any correlation with the taking of calcium and vitamin D supplements, or with the changes in the PCR. Possibly this fact is due to a direct action of the anti-TNF agent on osteoclastogenesis, through the activation of NFκβ, promoting apoptosis by means of caspase[58]. Another retrospective study with 45 patients with Crohn's (15 treated with infliximab and 30 controls), found and improvement in lumbar bone mass in the long term (measured using two DXAs separated by at least a year), independently of their nutritional state or of taking GC[59].

Finally, Miheller et al, assessed the possible effects of treatment with infliximab in 29 patients with CD on parameters of bone formation and resorption, and their possible relationship to changes in the OPG/RANKL/RANK system. These authors discovered an increase in the parameter of formation measured (OC) and a decrease in OPG (more in responders), at the same time as a decrease in the parameter of resorption measured (CTX) and an increase in RANKL, while the changes in these were not statistically significant. The authors conclude that the high levels of OPG could reflect a counter-regulatory response to factors such as inflammatory citoquines, or could indicate an activation of the T lymphocytes, thus justifying its diminution by the anti-inflammatory action of infliximab[60].

To date, there are no studies in the literature which have evaluated the affect of adalimumab on the bone metabolism of patients with CD (this drug is not yet approved for CD). However, a study with 50 patients with rheumatoid arthritis treated with adalimumab did not find changes in BMD (neither in the lumbar spinal column not in the femoral neck) over the course of a year, the authors concluding that the blocking of TNF-α could stop the loss of bone mass[61].

Conclusions

Patients with IBD show an increased risk of osteopenia and osteoporosis, and epidemiological studies have shown a high prevalence of low bone mass in these patients. Even though osteoporosis in these patients, which seems to be of high turnover, presents a multifactorial etiology, the inflammatory process which takes place in the intestines has now acquired a preponderant role. A better knowledge of the basic processes which take place at the level of bone, in this context of intestinal inflammation, could provide new therapeutic targets which could control, simultaneously, both sides of the coin (like, for example the anti-TNF drugs), permitting a better control for those patients with IBD, and thus improving their prognosis and quality of life.

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Patient of 92 years with gouty arthropathy

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Introduction

Gout is a metabolic disease characterised by the deposition of monosodium urate crystals in the interior structures of the joints. Its prevalence is approximately 8.4 cases per 1000 individuals and is more frequent in middle-aged and older males[1].

Although hyperuricemia is a necessary predispositional factor, its presence does not always imply the development of gout. In fact, the majority of hyperuricemic patients never develop gout[2,3,4]. Individual differences in the formation of the crystals or in the inflammatory response, or in both, could play a role in determining if a patient with hyperuricemia will develop gout. Unfortunately, there is not yet a satisfactory explanation for some of the clinical aspects of acute gout, including[5,6,7,8] the precipitation of acute attacks by trauma or surgery, its predilection for the first metatarsal-phalangeal joint, and the spontaneous resolution of the attacks.

The clinical manifestations of gout include recurrent attacks of acute inflammatory arthritis, accumulation of monosodium urate crystals in the form of tophaceous deposits, nephrolithiasis caused by the uric acid and chronic nephropathy. Three classic stages are described in the natural history of the progressive deposition of monosodium urate, which includes acute gouty arthritis, an interval, or intercritical gout, and then chronic tophaceous gout.

Acute gouty arthritis generally occurs some years after a period of asymptomatic hyperuricemia. A typical attack, which is markedly inflammatory, consists of severe pain, reddening, swelling and functional impairment which reach their maximum intensity after a few hours. In general (80%), the initial attacks only affect a single joint, typically in the lower extremities, often at the base of the big toe (*podagra*), or the knee. The associated signs of inflammation frequently extend beyond the affected joint and at times, can affect a number of joints, with tenosinovitis, dactilitis and even celulitis also apparent.

Overall, it has been observed that 12-43% of patients with episodes of gout show normal or even reduced values of uric acid in the blood[9,10,11].

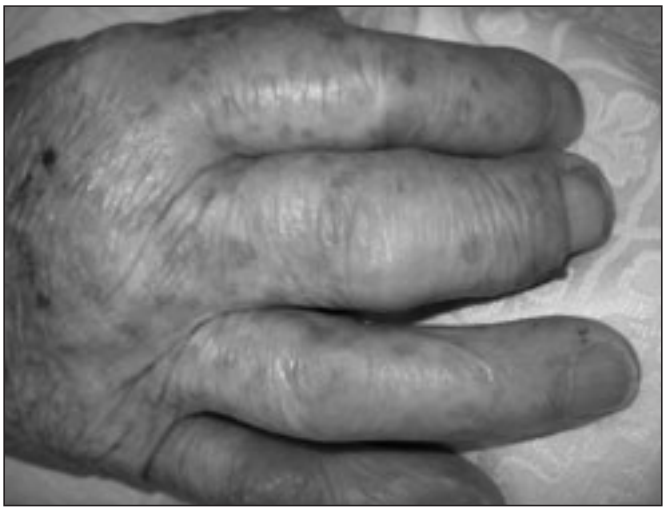

Figure 1. Image in which one can observe the presence of dactilitis as a result of arthropathy gotosa

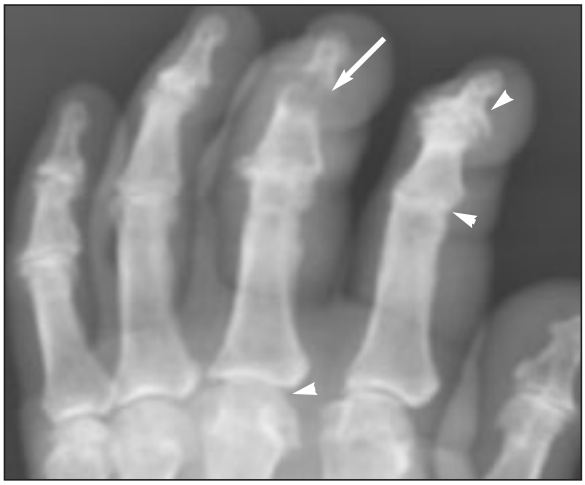

Figure 2.1 X-ray film of the left hand where signs of narrowing of the articular interline (arrow heads), and reabsorption of the third interphalangeal joint (arrow) can be seen

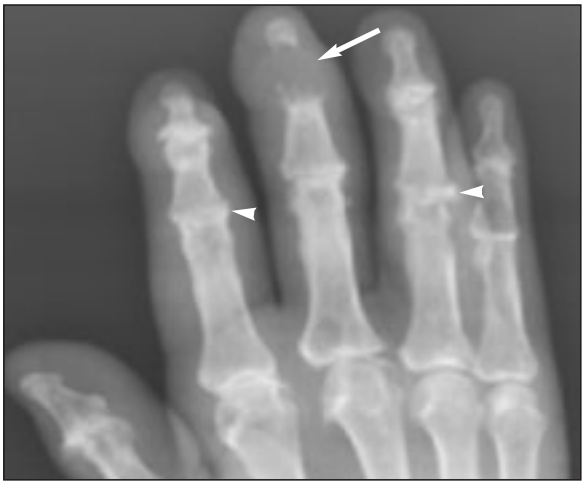

Figure 2.2 X-ray film of the right hand where signs of narrowing of the articular interline (arrow heads), and reabsorption of the third interphalangeal joint (arrow) can be seen

Radiological changes in chronic gout can show reduction in the height of the articular interline and the presence of highly characteristic erosions in the articular margins which are described as lytic lesions in the form of punch hole projecting into the edges of the bone (Martel's signs)[12]. During the first attacks of gout, and often also during the lifetime of the patient, in the radiography of the affected joint only tumefaction of the soft parts are observed.

Next, we present the radiological characteristics shown by a patient of 92 years of age with a history of arterial hypertension, which has developed over at least 5 years, a smoker until approximately 20 years ago, with packet–year index (IPA) of 150, diabetes mellitus type 2 which has developed for 5 years, being treated with oral anti-diabetics, dyslipidemia being treated with statins, chronic renal deficiency with levels of creatine habitually around 1.2-1.4 mg/dL, attributed initially to nephroangiosclerosis and diabetes mellitus, congestive cardiac failure diagnosed in the year 2005 and benign prostatic hyperplasia. The patient attended our service due to progressive dyspnea which had been developing over approximately 8 days until it practically became resting, and pleural effusion with characteristics of empyema was identified, which was treated with thoracic drainage and broad spectrum antibiotics.

The patient had a previous diagnosis of arthritis, troubling diffuse pain in multiple joints of several year's evolution. What also stood out was the *sausage-shaped* swelling *(dactilitis)* (Figure 1), especially in the third finger of the hand, and gouty tophi on the toes. On the third day of admission the patient described her pain: in the right knee, in the big toe of the left foot, and in both hands accompanied by tumefaction, erythematous coloration in the affected zones, and fever (despite the broad spectrum antibiotic given for her empyema). The analysis carried out at that time revealed levels of uric acid of 12.8 mg/dL, along with a real elevation in acute phase reactants (leukocytes: 15,000/mm^3 with 88% of neutrophiles, platelets: 1,096,000/mm^3; VSG 105 mm/h; fibrogen: 842 mg/dL; albumin: 2.5g/dL; PCR 330.8 mg/L. Treatment was started with colchicin (I mg every 4 hours) and her symptoms gave way in 24 hours, the patient showing a good tolerance to the drug, with no secondary effects.

On the X-rays a reduction in the articular interline could be observed, resorption of the third distal phalanx in both hands, an increase in the soft tissues and lytic lesions, suggestive of gouty arthropathy (Figures 2.1 and 2.2).

In this case the attack of gout appeared in the context of a minor surgical procedure[12], which is what a thoracic drainage is, and evolved satisfactorily, as is usual, 24 horas after starting treatment with colchicin.

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Hip fracture as the first manifestation of Cushing's Disease with genotype of Fabry's Disease

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Presentation of case

SLV is a woman of 35, who attended for a consultation for the first time in April 2008, having suffered a hip fracture.

Personal medical history: Arterial hypertension, with pre-eclampsia during her sole pregnancy which resulted in a cesarian section at 34 weeks, and at present controlled by medication.

Family medical history: Grandmother, father and sister with hypertension.

Start of the disease: The patient was found to be asymptomatic with adequate control of her arterial tension, until 17th November 2007, when, whilst going down the stairs carrying a load, the made a brisk movement of her right foot and noted a sensation of a "snap" in her right hip, without trauma and without falling over. She was seen the same day by a traumatologist who ordered an X-ray of her hip (Figure 1) on which no pathology was detected and from which the diagnosis of "torn muscle" was made, and for which he prescribed analgesics and rehabilitation, which the patient started to receive at a centre in this city.

The patient did not observe any improvement and attended the clinic again some days later. The rehabilitative doctor observed the existences of pain on the rotation, and limitations in the flexing, of the right hip, pain in when in the standing position, and the absence of contraction or haematomas. He requested a new X-ray of the pelvis (Figure 2) in which there were still no pathological signs, and he advised treatment with magnetotherapy, analgesics, pulsating ultrasound and by taking weight off the leg.

The patient continued to worsen, so an RMN of the hip was requested (Figure 3) in which was observed "bone oedema in the right femoral neck, with an oblique fracture without significant displacement of fragments (transcervical fracture, Pauwels type II), without changes in the morphology of either femoral heads". Treatment by resting the leg and with analgesics was prescribed. One month later the X-ray of the hip showed a radiological consolidation of the fracture with leg deformity, (Figure 4) for which was indicated a prgramme of rehabilitation, which included progressively increasing weight on the leg and hydrotherapy. For several months the patient followed the rehabilitative treatment, not observing any improvement in the pain. On the contrary, she noticed it worsening as soon she started putting weight on it.

In April 2008, the patient attended our Bone Metabolism Unit where a detailed clinical history was taken, which did not show any new details from those outlined earlier, the physical examination being normal (height: 157.5 cm. weight: 61 Kg. BMI: 24.7 Kg/m^2, arm span: 158 cm). We did not see the existence of the "buffalo hump", truncular obesity, wine-coloured stretchmarks, or any other characteristic signs of Cushing's Disease.

Figure 1. First X-ray of right hip, reported normal

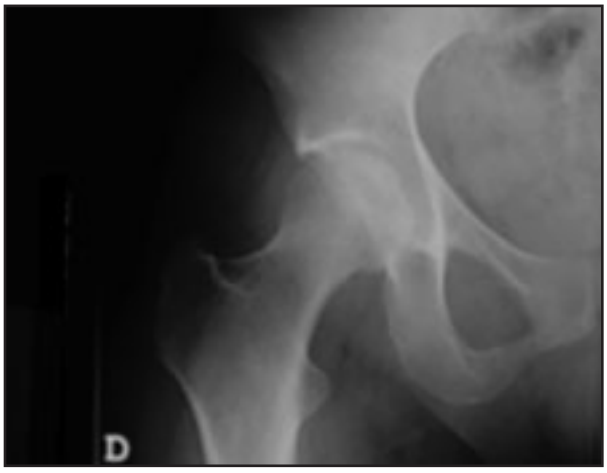


Figure 2. Second X-ray of right hip, also reported normal

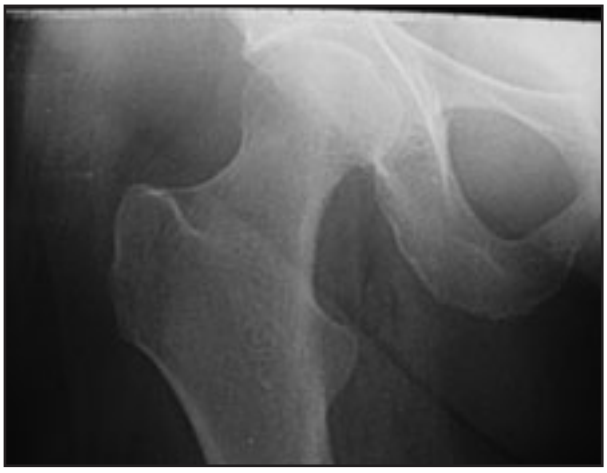
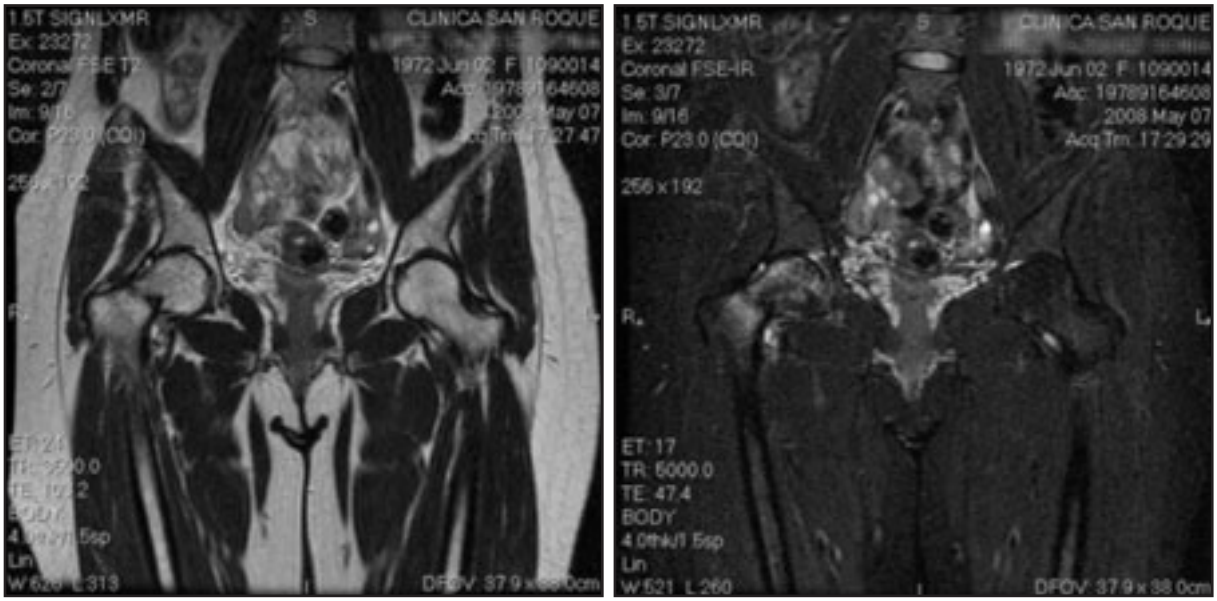


Figure 3. First RMN of hip, in which the oblique fracture is seen



A detailed analytical study was carried out, which was normal and which is shown in Table 1, a radiological study of the dorsal and lumbar spinal column, which did not show the existence of any vertebral fractures, and a bone densitometry in the lumbar spinal column and the proximal extremities of both femurs, and an estimation of the ultrasonographic parameters, also bilateral, whose values are shown in Table 2. Given the existence of pain when putting weight on the leg, and after almost a year of resting, a second opinion was requested from another traumatologist who, before the existence of the deformity in the femoral neck and the pain, suggested and carried out a surgical intervention, specifically a fixing, in situ, by means of an osteosynthesis with three cannulated screws by a minimum incision, to complete its consolidation. (Figure 5).

The patient began to put some weight on her leg with crutches and continued with aquatic physiotherapy. However, once she stopped using the crutches and started to put weight fully on her leg, the pain in the hip reappeared, a situation which lasted until December 2008, when pain in the lumbar region stated to appear – bilaterally, but more intense on the left side. A new RNM was carried out (Figure 6) which showed up the existence of a sacral fracture, on the left side. On this occasion there not been any trauma either. Some days later, pain in the right foot appeared and the gammagraphy carried out confirmed the existence of a fracture in the second right metatarsal. Both sacral and metatarsal fractures were diagnosed as "stress" fractures.

The patient was exhaustively re-evaluated and, among other complementary tests ordered, were a baseline cortisol test, and a suppression test with dexamethasone, as a genetic study to discount the possibility of diagnosing an illness of liposomal deposits. These results show the existence of

Figure 4. X-ray of hip. The consolidation with leg deformity is observed

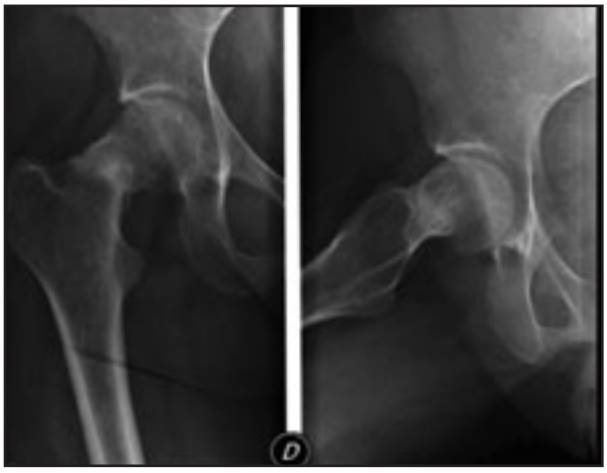


Figure 5. X-ray of hip after surgical intervention

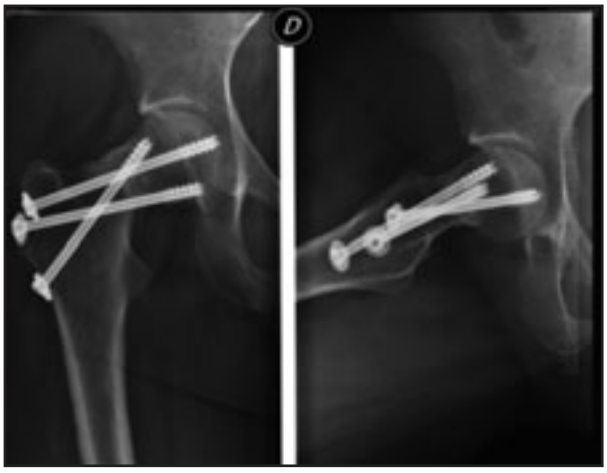
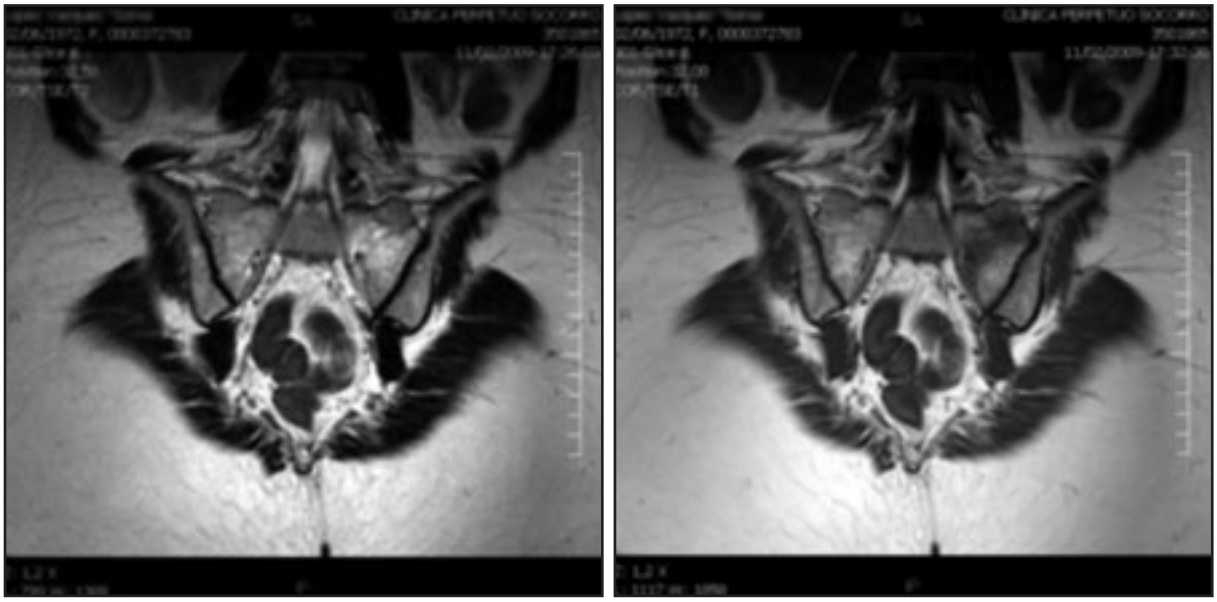


Figure 6. RNM of sacrum, in which is observed the existence of a new fracture



Cushing's Disease, confirming by RMN the existence of a hypophysary adenoma and a heterozygotic mutation in the GLA gene compatible with Fabry's Disease. Having completed the study the patient is on the waiting list for surgery.

Commentary

In this patient we were faced with two different clinical problems. In the first place, the appearance of a fracture of the femoral neck, as the first manifestation of Cushing's Disease, which on the other hand had not shown a single other clinical manifestation, save for arterial hypertension (well controlled by medication) without even being overweight (BMI: 24.7 Kg/m^2), and she was also a carrier of Fabry's Disease. The diagnosis of Cushing's Disease could only be made through an exhaustive search of secondary causes of osteoporosis, which did not even show clinical manifestations. Meanwhile, in addition to the fracture of the femoral neck the patient suffered two new fractures: one in the sacrum, the other in the fourth right metatarsal, which were initially considered to be "stress" fractures, the consequence of prolonged immobility the patient had suffered (more than one year), for treatment of the hip fracture.

The appearance of Cushing's disease in the form of various fractures, one of which being of the hip, in a young woman, has not been described until now in the literature we were able to consult. In itself, Cushing's Disease is an uncommon occurrence[1] and fractures can be a complication of this disease, but are usually late[2]. On the other hand, what calls ones attention as being atypical in this clinical case, is the practical absence of clinical manifestations of Cushing's, since the patient only showed HTA, which, what's more, was controlled with medication, in the context of a family with a wide history of HTA, her diagnosis being confirmed by the complementary test

Table 1. Some baseline data, related to bone mineral metabolism

Parameters (units)	Values
Calcium (mg/dL)	9.9
Phosphorus (mg/dL)	2.8
Total proteins (g/L)	7.4
PTH (pg/ML)	21.9
25-HCC (ng/mL)	18
PINP* (ng/mL)	16.5
Osteocalcin (ng/mL)	6
FATR** (UI/L)	2.4
Beta-crosslaps (ng/mL)	0.24
Urea (mg/dL)	26
Creatinine (mg/dL)	0.8
Na (U/L)	142
K (U/L)	4
Basal glucose (mg/dL)	93

* Amino-terminal procollagen type 1
** Tartrate-resistant acid phosphatase
All the values were within the limits of normality, with the exception of osteocalcin which was reduced (normal values between 11 and 43 ng/mL)

Table 2. Estimate of the bone mineral density in lumbar spinal column and both hips, and the ultrasonographic parameter in both heels

Anatomical location and (units)	Lower right member (fractured)	Lower left member
DXA		
Femoral neck (g/cm^2)	0.804	0.618
Tscore	-0.3	-2.0
Total in hip (g/cm^2)	0.653	0.710
Tscore	-2.4	-1.5
L2-L4 (g/cm^2)	0.888	
Tscore	-1.5	
Ultrasounds		
QUI	95.4	99.6
Tscore	-0.5	-0.2
BUA (dB/MgHz)	63.3	65.8
SOS (m/s)	1562.1	1572.6

carried out[3,4]. On the other hand, in the wide etiological search of the disease, we carried out a genetic study to confirm or deny diseases of storage, and obtained, to our surprise, a mutation in the same allele in heterozygocity for the GLA gene: heterozygote for the double mutation IVS4-16[a]>g; IVS6-22 c>t, also described as IVS+1704 a>g; IVS6+249 c>t[5], which indicated that the patient was a heterozygotic carrier of Fabry's disease with normal enzymatic activity (Alpha galactosidase in leukocytes: 61 nM/mgprot.h and Alpha galactosidase in blood: 20 nM/ mL.h).

Fabry's Disease, Anderso-Fabry or *angiokeratoma corporis diffusum*, is a hereditary disorder with the mutation of the alpha galactosidase A gene situated in the chromosome X (Xq 22.I). This mutation determines the storage of the neutral glycosphingolipids (globotriaosylceramide and galactosilceramides) in the lisosomes of the endothelial, perithelial and smooth muscle cells, with their accumulation in the blood. The incidence is of between 1/40,000 to 1/117,000 in the whole world[6], although in our environment it is one case for every 476,000 living persons (1:238,000 males)[7], and its distribution is pan-ethnic. Its clinical expressivity is usually more serious in males, although women carriers are not exempt from being affected[8]. The clinical spectrum is highly varied; from neutropathic pain, fever of unknown origin, intolerance to cold and hypohydrosis, corneal opacity, gastrointestinal affectation, angiokeratomas and tinnitus, to an affectation of the target organ with early cardiovascular disease, cerebrovascular accident, progressive renal failure to a terminal state, left ventricular hypertrophy and arrhythmia[9], without finding a single similarity with the clinical picture of our patient nor its sub-clinical detection through the complementary tests carried out. Manifestations less frequent are osteopenia and osteoporosis[10,11], with the description of an isolated case of avascular necrosis of the femoral head[12]. In this genetic study we found the same mutation in the mother and sister, with normal enzymatic activity in both. Neither had had fractures. There were no brothers.

We do not know to what extent Fabry's disease could have played a role in the appearance of these fractures or what may have been caused by co-existing Cushing's disease.

Secondly, the other clinical problem this patient had, was the delay in the diagnosis of the fracture of the femoral neck. The clinical data (young woman, previously healthy, minimum trauma), along with the fact that the first two X-rays did not detect the fracture, contributed to this happening unnoticed, and putting weight on a fractured neck produced a deformity of the leg, which finally required surgical treatment for its consolidation.

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1 Co-ordinator

2 Members of the Scientific Committee

(See Annex 1)

Osteonecrosis of the Jaw: Consensus document

*Consensus document of the **Spanish Society for Bone and Mineral Metabolism Research (SEIOMM)** in conjunction with: Spanish Association for the Study of the Menopause (AEEM), Hispanic Foundation for Osteoporosis and Metabolic Diseases (FHOEMO), Spanish Society of Mouth Surgery (SECIB), Spanish Society of Oral and Maxillofacial Surgery (SECOM), Spanish Society of Orthopedic Surgery and Traumatology (SECOT), Spanish Society of Endochrinology and Nutrition /SEEN), Spanish Society of Osteoporotic Fractures (SEFRAOS), Spanish Society of Geriatrics and Gerontology (SEGG), Spanish Society for Family and Community Medicine (SEMFyC), Spanish Society of Internal Medicine (SEMI), Spanish Society of Oral Medicine (SEMO), Spanish Society of Doctors in Primary Medicine (SEMERGEN), Spanish Society for Rehabilitation and Physical Medicine (SERMEF), Spanish Society of Rheumatology (SER), Ibero-American Society for Bone and Mineral Metabolism Research (SIBOMM).*

Summary

Our objective has been to write a position statement on the risk of developing maxillary osteonecrosis (ONJ) in patients receiving bisphosphonates for the treatment of osteoporosis, and identifying and evaluating the extent of the evidence which supports the recommendations. In order to do this we have reviewed the published studies on the definition, epidemiology, physiopathology, clinical manifestation, diagnosis and treatment of ONJ, producing, after their analysis, the current recommendations. These have been developed after a pre-agreed and reproducible process, which included an accepted model for the evaluation and citing of the evidence which supports them. The document, once produced by the co-ordinators, was reviewed and discussed by all the members of the panel, who produced draft recommendations which were finally studied and approved by the experts of the medical societies concerned with bone mineral metabolism, listed in Annex 2.

1. Introduction

Osteonecrosis is an infrequent clinical condition, associated with a change in blood supply or an inhibition in osteoblastogenesis and an increase in apoptosis of the osteocytes. In the past osteonecrosis has been associated with diseases such as lupus, falciform cellular anaemia (sickle cell anaemia) or Caisson's disease, or with certain treatments such as the use of corticoids or radiotherapy[1].

In 2003 and 2004 the first cases in patients who took bisphosphonates, of a process which was then named maxillary osteonecrosis (ONJ), were published[2,3]. Bisphosphonates are a group of drugs which are widely used in a large number of metabolic bone diseases, some of which are very frequent in the population of older people, such as osteoporosis. The initial cases of ONJ described were seen in patients who received very high doses of bisphosphonates, in the context of neoplasic disease with metastasis, there being very few cases described among patients receiving these drugs at doses used for osteoporosis. Even so, they generated alarm as much in the scientific community as in the general public. ONJ has a multifactorial etiopathogeny and has also been seen in patients who are not taking bisphosphonates. We have produced this position statement with the intention of clarifying the most controversial aspects of this matter.

2. Definition

The first problem which we encounter when we study ONJ is the absence of a clear and universally accepted definition of the disease. A panel of experts of the American Society for Bone and Mineral Research (ASBMR)[4] recently recommended using the definition of "an area of exposed bone which persists for more than 8 weeks in the absence of previous irradiation and/or metastasis in the jaw". The American Academy of Oral and Maxillofacial Surgeons (AAOMS) has published a very similar definition: patients may have ONJ if they have three requisites: 1) current or previous use of bisphosphonates; 2) presence of exposed or necrotic bone in the maxillofacial region which has persisted for 8 weeks; and 3) absence of maxillatory radiotherapy[5]. In Spain a panel of experts recommends the use of the following criteria for the definition of ONJ in neoplasic patients treated with intravenous bisphosphonates[6]:

1. The patient has received or is receiving treatment with intravenous bisphosphonate.
2. Presence of one or more ulcerous lesions in the mucous membrane of the alveolar processes, with exposure of the maxillary or mandibular bone. There may also be cases without bone exposure, with pain or fistulas, which should be considered as candidates for carrying out a more detailed study.
3. The exposed bone has a necrotic appearance.
4. The lesion occurs spontaneously or, more frequently, following dento-alveolar surgery (especially extractions).
5. Absence of scarring for a period of at least 6 weeks.

The development of these criteria is very important because it allows us to resolve one of the principal problems of ONJ: its identification and diagnosis.

3. Etiopathology

The etiopathology of ONJ is unknown. Nevertheless, a series of factors related to this disease has been described, as follows:

3.a. Changes to the immune system and in repair mechanisms due to neoplasia.
3.b. Vascular disorder
3.c. Low bone regeneration
3.d. Bone toxicity of bisphosphonates
3.e. Toxicity of bisphosphonates in soft tissues
3.f. Other

3.a. Changes to the immune system and repair mechanisms due to neoplasia

Neoplasia exists as an underlying disease in over 95% of patients with ONJ[7]. When metastasis is present neoplasia in itself increases the risk of infection and is associated with a change in the healing of the tissues[8]. On the other hand, patients with neoplasia normally receive medication which has an inhibitive effect on their immune system, such as immunosuppressors or corticoids; and all these, taken together, predispose cancer patients to the development of oral osteomyelitis or to suffering infections in places where dental extractions have been made. In fact, there is, in ONJ, an important infectious component, above all actinomyces[9]. However, it should be noted that all these factors have been present during the past decades, and, therefore, while they may contribute, they do not themselves explain the emergence of ONJ in the last few years.

3.b. Vascular disorder

Given that the disease has been named ONJ, it is stipulated that vascular disorder one of the keys in its etiopathogeny. While we don't know the etiology of ONJ, we do know that the reduction in the vascularization that may exist to a greater or lesser extent is not the only etiopathogenic factor. Thus, Hansen[9] has informed us that the vascular pattern in 7 out of 8 biopsies of patients with ONJ is normal, a finding similar to those described by other authors[10]. For some reason, which escapes us, there has been a tendency to equate ONJ with avascular bone necrosis in other locations, such as the hip, when there is no clinical or physiopathological parallel between the two conditions[7,11,12]. Since in patients with ONJ there is a change in the mucus membrane, the majority showing exposed bone, the possible effect of bisphosphonates on cell proliferation has been investigated. There is some evidence that high doses of bisphosphonates, for example zoledronate, inhibits such proliferation[13], but it is improbable that this effect might in itself be the principle etiological agent of ONJ.

3.c. Low bone remodelling

It has been suggested that a low bone remodeling could be an etiopathegenic factor which could contribute to the development of ONJ. Because of this the hypothesis is postulated that bisphosphonates, which act to inhibit bone reabsorption, used in a high dose in neoplasic patients (precisely those in which ONJ has most frequently been described) encourage the development of maxillary disease; however, it is difficult to confirm a hypothesis in which a reduction in bone regeneration may lead to a change in the healing of the soft tissues following a dental treatment.

In bone histopathological studies of patients with ONJ "frozen-bone" has not been observed. Various authors have described the existence of active reabsorption in over half of patients with ONJ[9,10]. Looking for similarities with other bone diseases, in primary hypoparathyroidism (in which there is low bone remodeling) no cases of ONJ have been described, however, in osteopetrosis there have been some accounts published of cases of osteomyelitis and osteonecrosis[14]. In these cases these lesions have been attributed to the obliteration of the bone medulla by sclerotic bone[15,16].

ONJ has been described only since bisphosphonates have been commercialised and used in daily clinical practice. During the development of clinical trials no cases of this disease were described. Only recently, with zoledronic acid, in the HORIZON study[17-19], was it confirmed that there was no increased risk of ONJ, since, in the end the study found 2 cases, one of which received the drug, and the other, the placebo. Finally, if the lesion is due to an inhibition of bone reabsorption, one needs to take into account the fact that new drugs for the treatment of osteoporosis, such as denosumab or catepsin K inhibitors, which also reduce to a significant extent bone regeneration, are being studied and in which, at least until now, no cases of ONJ have been found.

3.d. Bone toxicity of bisphosphonates

The bisphosphonates are drugs whose action on bone remodelling is to inhibit the activity of the osteoclasts. For this reason it had been thought that ONJ might constitute a manifestation in the bone of this suppression of bone remodelling, especially when high doses are used. Histological studies made in patients with ONJ have shown the existence of empty osteocytic lacunae[9], necrotic osteocytes[10], as well as lacunae containing healthy osteocytes. There are also studies which indicate that bisphosphonates reduce apoptosis in the osteocytes[20].

Since ONJ has been observed above all with the strongest bisphosphonates, administered intravenously[21] and at high doses, combined with the histological findings, has allowed the development of the hypothesis of direct toxicity of bisphosphonates on the bone. However, in contradiction to this is the fact that they affect only the maxillary, and not other, bones, on which the bisphosphonates act equally. On the other hand, no diminution in ability to repair fractures, either in patients affected by ONJ or in different tests carried out with bisphosphonates, have been described[18,22-25], while a recent cohort study showed a significant association between the use of bisphosphonates and pseudoarthritis in fracture of the humerus even though its incidence in absolute terms is minimal[92]. Another study, Abrahamsen et al[93], found that more than 6 years of treatment with alendronate did not increase the risk of femoral fracture.

3.e. Toxicity of bisphosphonates in the soft tissues

Another theory which has recently been published is that the bisphosphonates accumulate in the alveolar bone, both in the jaw as well as in the maxillary bone, producing toxicity in the surrounding soft tissues[32]. The bisphosphonates don't only act on the bone (although it is on bone tissue that they fundamentally act), but also on other cells. On the one hand, the reaction of the acute phase which usually occurs following the intravenous administration of bisphosphonates produces an inhibition of the farnesyl-pyrophosphate-synthase (FPPS) enzyme, which, in the monocytes, induces the activation of the Tγ,δ cells[26]. Similar effects have been described in other cells such as microphages, endothelial cells, tumour cells and osteoblasts[27]. These effects are related to the strength of the bisphosphonates and the amount of time that the cells are exposed to these drugs, which suggests a gradual accumulation in these cells of these drugs over time[7,11,12]. Another study has shown that the proliferation of existing osteoblasts in the periodontal ligament is reduced as the concentration of alendronate in a cultivated medium is increased[28]. In macrophages and other cells, the bisphosphonates penetrate through a process of endocytosis[29] which is unidirectional, and because there is no mechanism of eliminating the drug, will lead to its accumulation.

Finally, what should also be taken into account is that the possibility of gastrointestinal inflammation, oesophagitis and ulcers has been very well documented, observed most often when the bisphosphonates are administered daily by mouth. This secondary effect probably represents a toxicity by contact similar to the oral ulcerations observed when bisphosphonate pills are sucked[30].

3.f. Other

On the other hand, Kamaishi, et al[31] published in 2007 a series of 31 cases of which 18 (58%) were diabetics or those who had altered levels of glucose when fasting, while in the control group, consisting of cancer patients treated with bisphosphonates and without ONJ, the prevalence of diabetes was 12%, and the general population, 16%. In these patients, in two cases (6.4%) neoplasia was not present as an underlying disease (one had osteoporosis and one had rheumatoid arthritis). The authors conclude that diabetes can be a risk factor for ONJ and suggest possible physiopathological mechanisms by which diabetes can increase the effect of the bisphosphonates.

These etiopathogenic factors are not mutually exclusive. In fact is it possible that ONJ might be a disease whose etiopathogeny is multifactorial[7,11,12,32]. On the other hand, it should be noted that in up to 70% of cases the patients had undergone a dental intervention: extractions, implants, etc.[2,3,7,10-12,21,32-34], although in 30% ONJ is observed without such an intervention.

4. Epidemiology

Here we set out information regarding the epidemiology of ONJ, which we have been able to obtain in various ways: a) description and review of cases; b) studies of prevalence based on population; and c) data obtained from pivotal studies.

4.a. Description and review of cases

The first publication of cases of ONJ was produced in 2003 by Marx et al[2]. These authors collected a total of 36 cases of ONJ. All these cases were receiving intravenous bisphosphonate –pamidronate and/or zoledronate– in high doses. In all these cases neoplasia was present as the underlying condition, with the exception of one case of osteoporosis (2.7%). Since it was only a letter to the editor neither the dose or the period of time that the bisphosphonate was given to the patient affected by osteoporosis was specified. One year later, in 2004, Ruggiero et al[3] gathered a total of 63 cases of ONJ, which to date constitutes one of the most important groups of patients. Of these 63 cases, the underlying disease was osteoporosis in 7 patients (11.1%), the rest being cancer patients.

Since then a large number of articles have been published, the majority containing descriptions of isolated cases or series of cases, more or less short[35,36-66]. In these publications the risk factors most frequently found are the presence of underlying neoplasia, which is present in 95% of cases, and the intravenous administration of bisphosphonates[67,68]. Zoledronate is a 3rd generation bisphosphonate which is administered intravenously, and is at present the most potent bisphosphonate available[69]. Thus most of the cases of ONJ are associated with this drug, above all after its commercialisation and almost systematic use in patients affected by neoplasia in whom, clinically, there is a high risk of hypercalcemia and/or bone metastasis, such as occurs in multiple myeloma, prostate cancer, breast cancer and lymphatic cancer[4].

The working group on ONJ of the American Society for Bone and Mineral Research (ASBMR) carried out a review of cases of ONJ published in PubMed and Medline and found a total of 57 cases of ONJ in patients treated with bisphosphonates for osteoporosis and 7 cases in patients affected by Paget's disease. Of the 57 cases of osteoporosis, most had received alendronate, two risedronate, one a combination of alendronate and risedronate, and two pamindronate and/or zoledronate intravenously. The conclusion of the working group was that the risk of ONJ associated with therapy with bisphosphonates for osteoporosis was between 1/10,000 and 1/100,000 patients/treatment years[70].

4.b. Prevalence studies based on population

Two broad studies have been published of patients receiving bisphosphonates and both have confirmed that the risk of ONJ in patients who do not have cancer is very low:

- A study carried out in Germany, which included 780,000 patients who received bisphosphonates for osteoporosis, found three cases of ONJ, with a prevalence estimated at 0.00038%, which equates to the risk of one case for each 100,000 patients per year[71]. This study has the limitation that the diagnosis of ONJ could not be verified.

- On the other hand, Australian researchers carried out a postal survey looking for cases of ONJ related to bisphosphonates. They obtained 154 cases of which 114 had neoplasia, 8 Paget's disease and 36 osteoporosis. All the patients in the osteoporosis group had received alendronate. They estimated a frequency of ONJ of between 0.04% and 0.01%, increasing to between 0.09% and 0.34% in patients having had an extraction. The study had many methodological limitations, such as, for example, the fact that the information used was gathered using the post without the ability to confirm, or not, the existence of ONJ, and without the ability, also, of excluding the possibility of duplicate cases; in addition, they only collected cases from the public medicine system and none from the private medicine system[22-24,72-74].

4.c. Randomised clinical trials

Given that ONJ was a disease which did not used to be associated with the drugs when the pivotal studies were carried out with the different bisphosphonates, information which could have been produced in these studies is not available with either etidronate, alendronate, risedronate or ibandronate[18]. Neither were the trials designed to record adverse secondary effects in the oral cavity.

On the contrary, in the HORIZON study, which is pivotal for zoledronic acid, possible cases of ONJ were recorded. This study, carried out on 7,736 women, administered 5 mg of zoledronate to the treated group and a placebo to the control group, supplemented by calcium and vitamin D in both groups. At the end of the study two cases of ONJ were found, one in each group, from which it was concluded that zoledronic acid at the dose used for the treatment of osteoporosis (5mg intravenous, annually) does not increase the risk of ONJ[5,17].

5. Clinical stages of ONJ

The AAOMS has described the following clinical stages in ONJ[75]:

Stage I The presence of exposed or necrotic bone in asymptomatic patients, with no evident signs of infection.

Stage II The presence of exposed or necrotic bone in patients, with pain and evident signs of infection.

Stage III The presence of exposed or necrotic bone with pain, infection and one or more of the following signs: pathological fracture, extra-oral fistula or osteolysis extending to the lower edge.

6. Diagnósis

The first problem we have at present in diagnosing ONJ is the absence of a universally accepted, single definition of the disease. For this reason we must opt for that which adapts best to our clinical circumstances.

The panel of experts of the ASBMR recommends differentiating between a **confirmed case**, which is defined as an area of exposed bone in the maxillofacial region which is not cured after 8 weeks after its identification by a specialist, in a patient being treated with bisphosphonates and who has not received craniofacial radiotherapy treatment. 8 weeks is the period of time in which most traumas, extractions and surgical procedures which could damage the soft tissues, are healed. In cases in which the lesion might have appeared spontaneously, or in which the period over which it has developed is not known, the period of 8 weeks starts from the moment at which the specialist (doctor, odontologist) had documented the lesion. A **suspected case** would be when the same circumstances as above have occurred but in which the 8 weeks have not passed. These suspected cases should be kept under observation until the confirmation, or not, of the existence of ONJ[76].

6.a. Biochemical markers for bone remodelling and ONJ

In a study published by Marx et al[76], the authors found that the biochemical marker for bone remodelling was "telopeptide C-terminal of collagen type I" in the blood (CTX) when fasting, and observed that there was a correlation between its levels and the length of period of use of oral bisphosphonates, suggesting that an increase in values of CTX in the blood could indicate a recuperation of bone remodelling, which happens when the treatment with bisphosphonates is suspended. In addition, they stratified the relative risk of suffering ONJ in such a way that values of CTX lower than 100pg/ml would represent a high risk, values of between 100pg/ml and 150pg/ml indicate a medium risk and values over 150pg/ml, a low risk. Levels of CTX in the blood increase by between 25.9 and 26.4pg/ml for each month of a break in therapy indicating, according to the authors, a recuperation of bone remodelling. High values of CTX in the blood – above 150pg/ml - could be used as a guide for oral surgery procedures since the authors observe healing of mouth lesions either spontaneously or after receiving the appropriate treatment, or, on the other hand delaying mouth surgery in those patients who have levels of CTX in the blood lower than 150 pg/ml. This study has since been criticised by other authors who do not agree with the recommendations made by Marx et al[4,77,78]. This includes the ASBMR working group which having recently published a position paper on ONJ[79], published an *addendum* in which they clarified that CTX blood level values could not be taken as a "golden rule" which enables the prediction of the development, or not, of ONJ following dental surgery[80].

7. Already-established treatment of ONJ

The already-established medical and surgical treatment of ONJ can be found in numerous guides to clinical practice, both national[6,81-83] and international[4,75,84-86], to which the interested reader are referred, since it is moving away from the objectives of this document.

8. ONJ as a complication in the treatment of osteoporosis

Most cases of ONJ are observed in patients who have underlying neoplasia, those most frequent described being multiple myeloma, breast cancer, prostate cancer, and others[4].

The few studies that are available have confirmed that the risk of ONJ in patients receiving bisphosphonates for osteoporosis is very low, in the order of 1 case per 100,000 prescriptions of bisphosphonate. So, the ASBMR working group estimates that the risk of ONJ associated with therapeutic use of bisphosphonates for osteoporosis was between 1/10,000 and 1/100,000 patient/treatment years[87]. As mentioned in the previous section, in the work published in Germany, they found a risk of 1 case in every 100,000 patient years[71] and in Australia it was between 1 and 4 cases for every 10,000 patients[17-19].

On the other hand, the HORIZON study, the only study which has documented the appearance of ONJ as an adverse effect, did not find an increase in the risk of ONJ in patients receiving bisphosphonates, in this instance intravenously[86].

9. Position statements and clinical guides from medical, surgical and odontological societies concerning ONJ

The expert authors of position statements and clinical guides have agreed in general, on two facts: on the one hand they recognise the scarceness of scientific evidence, and the need, therefore, to make recommendations based on the opinions of experts; and on the other hand, there have recently been published, in a short period of time, updates which are largely converging in the view that the risk of ONJ from bisphosphonates utilized at doses used for the treatment of osteoporosis is very low, when previously they had issued warnings on this matter.

The American Association of Oral Medicine published in 2005 a position statement which indicated that patients who were at risk of developing ONJ were those suffering from multiple myeloma or metastatic cancer patients in whom intravenous bisphosphonates were used, but also in patients receiving bisphosphonates for osteoporosis. They recognised the lack of clinical guides based on evidence and that those that did exist were based on the opinion of experts[84].

Recently, in December 2008, the American Dental Association (ADA) published an updated version of their recommendations for the management of patients receiving bisphosphonates by mouth. This document updates the recommendations made by this association in 2006. Following a detailed review of available literature, the ADA indicates that the risk of developing ONJ apparently remains low. In addition, they say that we do not have the direct evidence to identify patients at high risk of developing this complication. In another document also published by the ADA, specifically on the dental management of those patients who are receiving bisphosphonates, the authors conclude that there is not a single piece of evidence of any kind and, therefore, state that stomatologists and odontologist should act "following their own criteria"[88].

The Canadian Association of Oral and Maxillofacial Surgeons (CAOMS) published a position statement in 2008[89]. This document pays much attention to the previous state of oral hygiene of the patient. In patients with adequate oral health the authors state that there is absolutely no problem with initiating treatment with bisphosphonates, be it oral or intravenous, providing that there is a six-monthly check up[89]. If preventative mouth care has not been carried out or if there is a dental emergency, these problems should be resolve before the start of treatment with bisphosphonates. If patients are already receiving bisphosphonates and present with a real dental emergency, invasive surgery should not be delayed, although consideration should be given to suspending the bisphosphonate treatment during the period of healing. For patients who require non-emergency invasive dental treatment, the bisphosphonate treatment should be interrupted for some months before the intervention until the wound is healed. However, we did not find any clinical studies which concerned themselves with the convenience, or not, or with the duration, of this interruption of treatment.

In Spain some consensus documents have been published, sponsored by Professor Bagan[6,81], and others by different societies such as the Spanish Society for Oral and Maxillofacial Surgery[83]. The first, from 2006[82], centred on patients with neoplasia and having intravenous bisphosphonates, brings together recommendations as much for the prevention as specifically for the treatment of already established ONJ, even proposing a form for gathering data in a uniform way. In this first document it is recommended that, when a patient receives intravenous bisphosphonate at doses used for neoplasia, they should be monitored by the odontologist/stomatologist at least once a year, to detect, and in which case, treat, caries and periodontal disease at an early stage.

In an later work Balgan, et al[6] promoted a protocol for those patients who are going to start treatment with intravenous zoledronic acid for their neoplasic pathology, which were previously evaluated and treated by an oral hygiene professional.

ANNEX 1

Co-ordinator

Manuel Sosa Henríquez

Members of the Scientific Committee

- Manuel Sosa Henríquez, President SEIOMM
- María Jesús Gómez de Tejada Romero, Secretary SEIOMM
- Esteban Jódar Gimeno, Treasurer SEIOMM
- Javier del Pino Montes, Vice-President SEIOMM
- Adolfo Díez Pérez, Ex-President SEIOMM, Vice-President SEFRAOS
- Manuel Díaz Curiel, Ex-Treasurer SEIOMM, President FHOEMO
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- José Vicente Bagán Sebastián, Professorial Chair of Medicine of the Mouth, Universidad de Valencia. Director of the Stomatology Service, Hospital General Universitario de Valencia

ANNEX 2

Co-ordinator
Spanish Foundation for Bone and Mineral Metabolism Research (FEIOMM)
Spanish Society for Bone and Mineral Metabolism Research (SEIOMM)

Scientific Societies
Societies which participated in this position statement:
- Spanish Association for the Study of the Menopause (AEEM)
Reviewer and President: Javier Ferrer Barriendos
- Hispanic Foundation for Osteoporosis and Metabolic Diseases (FHOEMO)
Reviewer and President: Manuel Díaz Curiel
- Spanish Society of Mouth Surgery (SECIB)
Reviewer and President: José Mª Martínez-González
- Spanish Society of Oral and Maxillofacial Surgery (SECOM)
Reviewer and President: Rafael Martín-Granizo López
- Spanish Society of Orthopedic Surgery and Traumatology (SECOT)
Reviewer: Fernando Marco Martínez, President: Enric Cáceres Palou
- Spanish Society of Endochrinology and Nutrition (SEEN)
Reviewer: Manuel Muñoz Torres, President: Tomas Lucas Morante
- Spanish Society of Osterporotic Fractures (SEFRAOS)
Reviewer: Adolfo Díez Pérez, President: Antonio Herrera Rodríguez
- Spanish Society of Geriatrics and Gerontology (SEGG)
Reviewer: Carmen Navarro Ceballos, President: Pedro Gil Gregorio
- Spanish Society for Family and Community Medicine (SEMFyC)
Reviewers: José SanFélix Genovés / Vicente Giner Ruiz, President: Luis Aguilera García
- Spanish Society of Internal Medicine (SEMI)
Reviewer: José Antonio Blázquez Cabrera, President: Pedro Conthe Gutiérrez
- Spanish Society of Oral Medicine (SEMO)
Reviewer and President: Antonio Bascones Martínez
- Spanish Society for Doctors in Primary Medicine (SEMERGEN)
Reviewer: Carmen Valdés Llorca, President: Julio Zarco Rodríguez
- Spanish Society for Rehabilitation and Physical Medicine (SERMEF)
Reviewers: Elena Martínez Rodríguez / Andrés Peña Arrébola, President: Inmaculada García Montes
- Spanish Society for Rheumatology (SER)
Reviewer: Javier del Pino Montes, President: Rosario García de Vicuña
- Ibero-American Society for Bone and Mineral Metabolsim Research (SIBOMM)
Reviewer and President: Daniel Salica

Position statement of the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM), and societies related to bone mineral metabolism, on osteonecrosis of the jaws and bisphosphonates used in the treatment of osteporosis

Materials and Methods

The methodology which has been followed has been that of the consensus of the panel of experts. The document generated has been sent to the scientific societies listed in Annex 2. The suggestions or amendments made have been raised with the panel of experts, who have accepted or rejected them, before being re-presented for their reappraisal by the participating societies. The final document brings together the results of this whole process.

Questions produced by the panel of experts

The panel of experts, who met to review the first part of this document, raised the following questions:

1. What is the risk of a patient who is being treated with bisphosphonates for their osteoporosis suffering ONJ?

2. Is there a profile of a patient being treated with bisphosphonates for their osteoporosis, which could be at higher risk of developing ONJ if they were going to undergo a dental operation?

3. Should bisphosphonate treatment be suspended before any such dental operation?

4. Is there any complementary test which allows the establishment - unequivocally, or with a high margin of safety – the risk of suffering ONJ?

Recommendations of the panel of experts on the risk of ONJ in patients receiving bisphosphonates for the treatment of osteoporosis

1. It is estimated that the risk of developing ONJ in the context of treatment of osteoporosis is in the region of 1 case for each 100,000 patient/years.

2. Although the risk of ONJ in patients treated for osteoporosis is very low, a series of factors associated with a higher risk of ONJ have been described (Table 1). The predictive ability of each

of these factors is not established and is extremely low in terms of absolute risk.

The panel considers that, among patients treated with bisphosphonates at the doses used for osteoporosis, those with a previous history of ONJ, those being treated with immunosuppressors and those undergoing prolonged treatment with bisphosphonates have a higher risk of developing ONJ.

3. Conservative odontological treatment can be carried out at any time without previous suppression of treatment with bisphosphonates: on the other hand:

3.a. In patients who are taking bisphosphonates at the dose required for the treatment of osteoporosis for less than 3 years and who don't have additional risk factors, it is not necessary to change or delay surgery if it is required. This includes all odontostomatological surgery. These patients should be attend periodical reviews.

3.b. In cases in which individuals are taking bisphosphonates at the dose required for treatment of osteoporosis for less than 3 years and at the same time are having therapy with corticoids, contact should be made with the prescribing doctor to evaluate the possibility of suspending the bisphosphonate treatment at least 3 months before the oral surgery, except if the risk of fracture in the patient is high (age > 70 years, presence of previous fracture, densitometry with T-score <-2.0), in which case it is not necessary to suspend treatment. In case of suspension, the treatment should be reinstated as soon as healing occurs.

3.c. In patients who are taking bisphosphonates at the dose required for treatment of osteoporosis for more than 3 years, who are those most in need of treatment for this disease, it is necessary to especially evaluate the risk of bone fracture and compare it with the risk of ONJ. The prescribing doctor should be contacted to consider suspension of treatment at least 3 months before surgery, except when the risk of a fracture in the patient is high (age > 70 years, presence of previous fractures, T-score < -3,0) in which case it should not be suspended. In case of suspension, the treatment should be reinstated as soon as healing occurs, see algorithm on page 49.

4. The panel had the view that not a single complementary test has shown the sensitivity or specificity for the prediction and early diagnosis of ONJ. Some authors have recommended the use of blood sCTX as a marker for risk, but at present there is no solid scientific evidence which validates its use. The reasons are[90]:

a) The values proposed as indicating high risk of suffering ONJ are within the range of reference of sCTX in premenopausal women who are healthy and not in treatment, even if there is a significant variation in the ranges of reference according to different studies and analytical methods.

b) For the interpretation of the values of sCTX the co-efficient of variation (CV) needs to be taken into account, which integrates the analytical and biological variabilities. In the case of sCTX this CV is high.

c) The CV determines the minimum significant change or critical difference, which is the minimum change (in %) in the value of the marker between two consecutive demarcations which indicate a real and significant change in the activity of the process. The minimum significant change of sCTX is not well established, varying between 30 and 60% according to different studies.

d) Different commercial kits for sCTX give disparate results. It is necessary to establish standardised laboratory protocols to determine the CV, to calculate the minimum significant change and to establish well defined ranges of reference for sCTX.

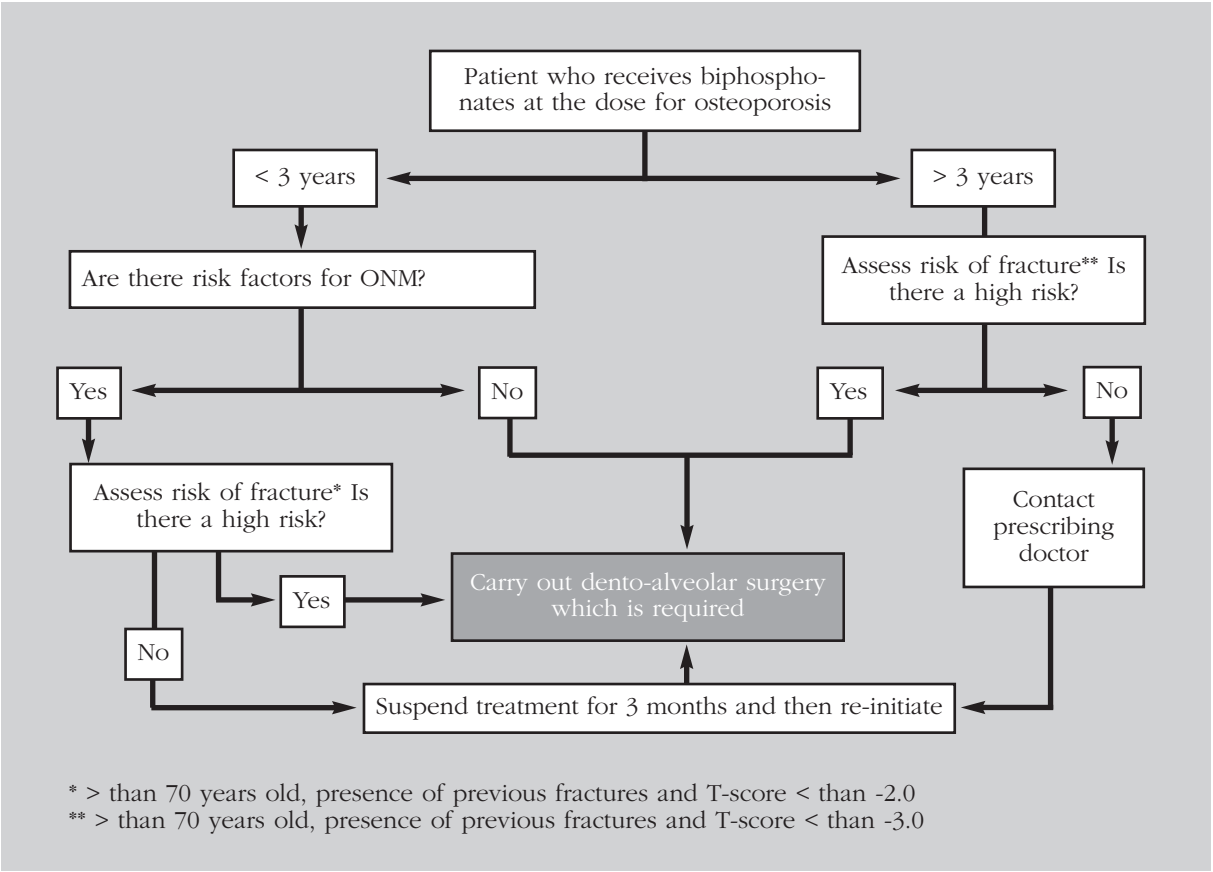
e) There are no controlled studies available which guarantee the use of sCTX as a predictive marker for ONJ. The predictive ability of sCTX for ONJ should be explored through ROC curves to identify sensitivity, specificity, positive predictive value and negative predictive value.

Table 1. List of risk factors described as being associated with ONJ*[91]

-Chemotherapy
-Cancer
-Immunotherapy
-Diabetes mellitus
-Female sex. Oestrogens
-Changes in coagulation
-Infections
-Tobacco
-Dental risk factors: periapical pathology, periodontal disease, dental abscesses, surgical procedures which affect the bone, trauma caused by poorly adjusted dental prostheses
-Drepanocytosis
-Systemic erythematous lupus
-Variations in atmospheric pressure
-Haemodialysis
-Hypersensitivity reactions
-Hypothyroidism
-Storage diseases
-Corticoids
-High blood pressure
-Arthritis
-Blood dyscrasias
-Vascular disease
-Alcohol abuse
-Malnutrition
-Advanced age
-Gaucher's disease
-HIV infection
-Chronic inactivity
-Hyperlipidemia and fat embolism
-Osteoporosis
-Neurological damage

**Factors listed in at least one publication, without there being a clear differentiation between those patients treated with bisphosphonates for neoplasia as for osteoporosis.*

Algorithm



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Committee of Experts of SEIOMM for the production of the guides
(See Annex 1)

Clinical Practice Guidelines for Posmenopausal, Esteroid and Male Osteoporosis

Introduction

When the last version of the "Clinical Practice Guidelines for Posmenopausal, Esteroid and Male Osteoporosis", Society of Bone and Mineral Metabolism Research[1] was produced it was agreed that it should be revised at least every 5-6 years, by editing a new version of the same document. At an intermediate point –at around 2-3 years– an update should have been produced, to include issues which could not wait for the editing of the new version, especially taking into account the fact that even as the second version was written the introduction to market of the new drugs was already being foreseen. The following document includes this update. It should be stressed that this should not be treated as an entire revision of the guides, rather only of some aspects –fundamentally therapeutic issues– considered most urgent.

Given that this should not be treated as a complete revision of the guides, rather only its update, we have considered it proper to take into account solely information relevant from the practical point of view; specifically, information related to the efficacy of the drugs in reducing the incidence of fractures. We have not assessed data related to substituted variables, such as Bone Mineral Density (BMD) or markers for bone turnover. However, we have included comparative studies or non-inferiority studies regularly carried out with BMD as a variable of efficacy, given that they definitely constitute an indirect way of establishing the usefulness of a particular drug –or in a particular way of administering them– for fractures.

Methodology

A systematic search of the bibliography in PubMed was carried out, with two different approaches: a) a search under "Theraputics", of the "Clinical Enquiries" section, using the names of the various drugs; b) a search starting with the MeSH terms, using the names of the various drugs, plus the terms "fracture" or "osteoporosis". The names of the drugs used in the searches were the following: etidronate, alendronate, risedronate, ibandronate, zoledronate, strontium ranelate, oestrogens, hormone replacement therapy, raloxifene, tibolone, calcitonin, PTH, parathormone, PTH 1-34, teriparatide, PTH 1-84, fluoride. The period of the bibliographic search started in January 2006, the point at which the systematic search for the second version of the guides ceased, and ended in December 2008. In addition to the works found in the systematic search over the aforementioned period, we also considered for this update information based on personal knowledge gained through regular handling of the bibliography related to this subject, and data presented at conferences; this information was included even though it was collected after the systematic search had been completed.

In order to assess efficacy in relation to fractures we analysed only works designed as clinical trials or meta-analyses, rejecting observational studies.

A first draft was written by the co-ordinator of guides (JGM), which was distributed among all the members of the Committee of Experts of the SEIOMM charged with producing the second version. They proposed changes to the document, according to which a second draft was produced, which again was sent to the members of the Committee. Finally, with the comments on this second draft the final, definitive version was produced, which was approved by the Committee. The document was submitted for the consideration of the scientific societies interested in osteoporosis.

Works selected

Postmenopausal osteoporosis

From the initial assessment of the works provided through the aforementioned bibliographic search, we considered of interest for inclusion in the current update the following: two non-inferiority studies of risedronate administered monthly[2,3], two meta-analyses of ibandronate[4,5] two clinical trials with zoledronate[6,7], a clinical trial of tibolone[8], another clinical trial of PTH 1-84[9], and three studies of strontium ranelate[10–12], the prolongation of SOTI[13] and of TROPOS[14].

With the desire to offer the most complete information, we have also included in this document works carried out with some drugs which are not yet approved for use in the treatment of osteoporosis, but of which there is data (published or communicated at conferences) on their efficacy in reducing osteoporotic fractures. For this reason we make reference to two clinical trials of both of the new SERM (bazedoxifene[15]) and another of denosumab[16], and a meta-analysis of fluoride[17].

1. Risedronate

The two non-inferiority studies published on risedronate administered monthly differ exclusively in the way the drug is administered: in one trial 75 mg. is administered in two consecutive days, while in the other 150 mg. is given in a single day.

1.1 Non-inferiority study which compares the effect of 75 mg. of risedronate administered on two consecutive days, once a month (150 mg. monthly) with that of 5 mg. daily[2].

This trial was carried out with 1229 women with postmenopausal osteoporosis, its principal objective being the assessment of changes in BMD in the lumbar spinal column over 12 months. The limit of the margin of non-inferiority was established at -1.5%. The group treated on the daily model increased its BMD by 3.6%, while in the group treated monthly the increase was 3.4%. The limits of the interval of confidence in the differences at 95% were -0.189 and 0.618%, in such a way that all the points of the aforementioned interval were found within the margin of non-inferiority.

1.2 Non-inferiority study which compares the effect of 150 mg. of risedronate administered one a single day per month, with that of 5 mg. daily[3].

This study is practically superimposable on the previous study, with the difference being in the monthly model for the administration of risedronate (150 mg. in a single day, instead of in two consecutive days). The number of women with postmenopausal osteoporosis included was 1094. The limit of the margin of non-inferiority was also established at -1.5%. The group treated on a daily basis increased its BMD in the lumbar spinal column by 3.4%, while in those treated monthly this increased by 3.5%. The limits of the interval of confidence in the differences at 95% were from -0.51 to 0.27%. So, in this case also, all the points of the aforementioned interval were found within the margin of non-inferiority.

Both trials have a level of evidence 1b, and in view of them the monthly theraputic regimen can be considered to be acceptable for risedronate (grade of recommendation, A).

2. Ibandronate

Two meta-analyses of the use of ibandronate have appeared, characterised by the use of the concept of an "accumulated drug dose" for those patients included in the trials at the end of a year of treatment. In those trials in which the drug was administered intravenously, the accumulated dose was considered to be the total administered by the end of one year. In the trials in which the drug was administered orally, the accumulated dose was considered to be 0.6% of the total dose administered over the same period. The two meta-analyses differed fundamentally in that the first[4] used historic controls, while the second one[5] did not. On the other hand, what they had in common was that in both cases the principal objective is non-vertebral fractures, and that these fractures were frequently picked up as adverse effects.

2.1 First meta-analysis

The patients in this first meta-analysis[4] could belong to four groups, depending on the quantity of the drug accumulated per year: a) ≥ 10.8 mg; b) 5.5-7.2 mg; c) 2.0-4.0 mg; d) 0 mg (placebo group). The outcome variables were: a) the main non-vertebral fractures (clavicle, humerus, wrist, pelvis, hip, leg); b) all non-vertebral fractures; c) all clinical fractures. The main results are derived from the comparison of the first (≥ 10.8 mg) and last (placebo) groups. The reduction in risk of the first type of fracture in the group with a total accumulate dose ≥ 10.8 mg. with respect to the placebo group was 34.4% (p = 0.032), that of the second group 29.9% (p = 0.041) and of the third group 28.8% (p = 0.010). The most important methodological limitation of this meta-analysis is that the patients assigned to the placebo group pertained to a different study from those in whom the accumulated dose was ≥ 10.8 mg. for which reason it should definitely be treated as a study with historic controls. On the other hand, the non-vertebral fractures were noted as adverse effects in half of the studies included in the meta-analysis. It being difficult to establish a firm grade of evidence for this work, we believe that in any case, in itself, it does not merit a grade of recommendation higher than C.

2.2. Second meta-analysis

The fundamental difference with the previous meta-analysis[4] is that in this one[5] the point of reference is not the placebo, but rather a daily dose of 2.5 mg. In the end, to avoid the historical character of the controls, the authors compare pairs of patients belonging to the same study. The study includes a greater number of trials. The principal outcome variables are the main non-vertebral fractures. In the main analysis comparison has been made between those patients with the highest accumulation of drugs (≥ 10.8 mg) and those with the lowest (5.5.mg). Another comparison was made

between those with the highest amounts and, those with the lowest and intermediate amounts combined. The accumulated dose of 10.8 mg or more corresponds to the combination of studies with 2 or 3 mg intravenously every 2 or 3 months (respectively), and with 150 mg. orally per month. The incidence of non-vertebral fractures is significantly less in the group with an accumulated dose of ≥ 10.8 mg than in that with an accumulated dose of 5.5 mg, with a hazard ratio (HR) of 0.621 (0.396-0.974). The result is similar if the high dose is compared with the combination of the low and the medium doses. Although this is a much more consistent work than the previous one, it retains the limitation that it supposes that the fractures are gathered as adverse effects. In fact the authors of the work themselves indicate that while the results are consistent with the idea that ibandronate is efficacious in the reduction of non-vertebral fractures, it does not provide the same level of evidence as a clinical trial, for which reason the level of evidence, in the best of cases, can not be more than 2a.

In the face of this meta-analysis, we conclude that a recommendation B can be given to ibandronate in as much as it refers to the diminution of non-vertebral fractures.

3. Zoledronate

Zoledronate has already been mentioned in the second version of the guides, but that was not considered to be the final assessment – neither was the algorithm included since the results of the pivotal study of women with postmenopausal osteoporosis (HORIZON-PFT)[6] had not yet been published. Here we comment on this work, together with another which included men and women, and which was carried out in patients with a fracture of the hip (HORIZON-RFT)[7]. This second study, therefore, does not strictly refer to postmenopausal osteoporosis, but rather to senile osteoporosis.

3.1 Pivotal study

This deals with a study[6] carried out in postmenopausal women with osteoporosis, and it is designed as a randomized, double blind, placebo controlled clinical trial. It was carried out with 7765 women with BMD ≤ -2.5 or ≤ -1.5 plus a moderate vertebral fracture or two light vertebral fractures. 21% of the patients was following treatment with other antiosteoporotic drugs distinct from the biphosphonates or PTH, such as sex hormones, raloxifene or calcitonin. The study lasted for 3 years and the patients were assigned either to the placebo or to 5 mg of zoledronate, i.v., annually. The primary objective was twofold: differences in the incidence of new vertebral fractures in patients who did not follow other concomitant antiosteoporotic treatment, and differences in the incidence of hip fractures in all patients. The secondary objectives were the development of other types of fractures (non-vertebral fractures, whichever clinical fractures, clinical vertebral fractures), changes in BMD (lumbar spinal column, femoral neck, the whole hip) and changes in the markers for bone turnover (CTX, bone alkaline phosphatase and PINP), as well as security data. The relative risk (RR) of morphometric vertebral fractures after three years was 0.30 (0.24-0.38). In the case of hip fractures the HR was 0.59 (0.42-0.83). Hence, with reference to non-vertebral fractures, the HR was 0.75 (0.64-0.87), in the combination of clinical fractures it was 0.67 (0.58-0.77), and in clinical vertebral fractures it was 0.23 (0.14-0.387). With respect to the adverse effects, important note should be taken of a higher incidence of what the authors named "serious auricular fibrillation" in the group treated with zoledronate (2.5% vs.1%, p<0,001). Together with this, and as is known from patients administered biphosphonates intravenously, patients assigned zoledronate presented a clinical picture of "pseudoinfluenza" or an "acute reaction phase", which affected approximately 30% of the population after the first injection, and at lower percentages at subsequent injections (around 6% at the second and 2% at the third).

3.2 Refracture study

This study[7] was carried out in patients of both sexes with a previous hip fracture. From the outset, it was designed to be randomised, double blind, and placebo controlled. On this occasion the study was carried out with 2127 patients (ratio of women to men – 75:25), they were followed for an average of 1.9 years. It was intended to continue the study until reaching fracture 211.The patients were assigned a placebo or 5 mg of zoladronate, i.v., annually. Their inclusion in the study took place within 3 months of surgical intervention. The primary objective was the appearance of new clinical fractures (excluding those in the face or the fingers). The secondary objectives were the appearance of new clinical vertebral and non-vertebral fractures, and fractures of the hip, as well as contralateral changes in the BMD of the hip, and security data previously established (including among them, mortality). The HR of all the new clinical fractures was 0.65 (0.50-0.84), that of the non-vertebral fractures 0.73 (0.55-0.98), that of the clinical vertebral fractures 0.54 (0.32-0.92), and that of the hip fractures 0.70 (0.41-1.19). In this trial no increase in auricular fibrillation in the patients treated with zoledronate was observed, however a beneficial effect of particular interest was detected: a reduction of 28% globally in mortality (from whatever cause) in the group assigned to zoledronate (p = 0.01). Logically, also observed were the manifestations of pseudo-influenza associated with intravenous biphosphonates, although in this case the incidence was significantly low (something less than 7% with the first injection and 0.5-1% with subsequent injections).

A *post hoc* analysis of this work[19] has studied whether the time elapsed from the suffering of the fracture to the administration of the drug can influence its effect. The results suggest that the drug is most efficacious if administered after two weeks because maybe if it is done earlier the drug tends to accumulate in the callous of the fracture.

Neither of the two trials spontaneously reported cases of osteonecrosis of the jaw bone. One earlier search directed especially at the detection of this complication in the pivotal study, signalled the possibility that there might be a case in each group.

Both trials have a level of evidence of 1b, which allows the assignation to zoledronate of the grade of recommendation A for the reduction of vertebral, non-vertebral and hip osteoporotic fractures.

4. Tibolone

A randomised, double blind, placebo controlled clinical trial has been carried out on tibolone[8] which included 4538 women from 65 to 85 years of age, either with BMD ≤-2.5 T in the hip or lumbar spinal column, or with BMD ≤-2.0 T plus vertebral fracture. They were assigned 1.5 mg of tibolone daily or a placebo. The primary objective was the appearance of new vertebral fractures, and the secondary objective the incidence of non-vertebral fractures, breast cancer, venous thrombosis or vascular disease. The study was interrupted at 34 months because of the appearance of serious secondary effects (ictus). The results can be summarised in the following way: HR of vertebral fracture, 0.55 (0.41-0.74]); HR of non-vertebral fracture, 0.74 (0.58-0.93); HR of invasive breast cancer, 0.32 (0.13-0.80); HR of cancer of the colon, 0.31 (0.10-0.96); HR de ictus, 2.19 (1.14-4.23). The authors' conclusion is that tibolone reduces the risk of vertebral or non-vertebral fracture, of breast cancer and possibly cancer of the colon, but increases the risk of ictus in older women.

The level of evidence in the trial is 1b, and as a result of this evidence we would discourage the use of tibolone in the treatment of osteoporosis in older women (> 65 years) and in women with risk of ictus (grade of recommendation A).

5. PTH 1-84

As we also commented on zoledronate, PTH 1-84 was already mentioned in the second version of the guides, but this was not considered as a final assessment because the results of the pivotal study[9] had not yet been published, nor had it been approved for commercial use. What follows is a more detailed account of this study.

It consisted of a randomised, double blind placebo controlled clinical trial which involved 2532 postmenopausal women who complied with one of the following criteria: A/ aged 45-54 years and I) BMD ≤ -3 T in the lumbar spinal column femoral neck or the whole hip, without vertebral fractures or II) BMD ≤ -2.5 T and 1-4 previous vertebral fractures; B/ aged ≥ 55 years and I) BMD ≤ -2.5 T without vertebral fractures, or II) BMD ≤ -2.0 T and 1-4 previous vertebral fractures. Approximately 19% of the patients presented with at least one vertebral fracture at the time they were included. The patients were assigned 100mg/d. of PTH 1-84 administered subcutaneously, or a placebo, for 18 months. The principal objective of the study was the appearance of new vertebral fractures and changes in the BMD. The RR for new vertebral fracture was 0.42 (0.24-0.72) and for non-vertebral fracture 0.97 (0.71-1.33). The percentage of women included in intention to treat analysis was 67.2%.

The level of evidence is 1b with a grade of recommendation A for the reduction of vertebral fractures.

6. Strontium ranelate

The results after 5 years[10] of the TROPOS study, whose results after 3 years[14] were already commented upon in the second version of the Guides, and whose principal objective was to study the effect of the drug on non-vertebral fractures, have been published. It was carried out as a randomised, double blind clinical trial in 5091 women who had been assigned 2g/d of strontium ranelate or a placebo over 5 years. At 3 years the RR of non-vertebral fractures had been reduced by 16%. A post hoc analysis carried out in women of 74 or more years with BMD in the femoral neck equal to or less than -2.4 T (reference: population NHANES III) showed a reduction of 36%. Vertebral fractures were reduced by 39%. The analysis at 5 years was planned in advance following the protocol. The number of women included in the intention to treat analysis was 97% of those originally included in the study, although the percentage who completed it was 53%. Those who were lost divided in a similar way in the two groups. The RR for non-vertebral fractures was 0.85 (0.73-0.99) and for the vertebral fractures, 0.76 (0.65-0.88). The post hoc analysis to assess the effect on hip fracture in high risk women showed an RR or 0.57 (0.33-0.97). The security profile of strontium ranelate was similar to those of the 3 year study.

There has also been published the results after 4 years[12] of the SOTI study[13], whose principal objective was to study the effect of strontium ranelate on vertebral fractures, and whose results after 3 years were also commented on in the previous version of the Guides. It consisted of a randomised, double blind, placebo controlled clinical trial carried out in 1649 postmenopausal women with at least one vertebral fracture. The group assigned to the treatment received 2g/d of strontium ranelate. At 3 years the RR for vertebral fractures had been reduced by 49%. The work on which we are now commenting presents the results of reduction in fractures at the fourth year. The intention to treat analysis included 87.6% of the women, with those lost at the end of the study at 30%. The RR for vertebral fractures was 0.67 (0.55-0.81). The RR for peripheric fractures was 0.92 (0.72-1.19). The original design of the study included an additional analysis at 5 years, after which half the women in the group having treatment moved to receiving the placebo, and all those receiving the placebo, received the treatment, but, this analysis at the fifth year was not intended to provide data regarding efficacy in fractures, but regarding the evolution of BMD.

Finally, data has been presented from a study[11] which analyses the effects of prolonging the ingestion of strontium ranelate over three years –in an open regimen– in women who had received the drug over 5 years in the SOTI or TROPOS studies[10,12]. The data refer exclusively to patients treated with strontium ranelate over 8 years, without there being a placebo group (all were treated from the start of the aforementioned studies, for four or five years). What is assessed in this work is the incidence of vertebral or non-vertebral fractures over these three years of prolongation, comparing it with their incidence during the first three years the patients were followed (that is, during the SOTI and TROPOS studies). The authors did not find significant differences, and concluded that this suggests that strontium ranelate maintains its efficacy in relation to both types of fracture over 8 years. The values for the incidence of the said fractures in both periods were as follows: for vertebral fractures, 13.7% for the last 3 years and 11.5% for the first 3; for non-vertebral fractures, 12.0% for the last 3 years and 9.6 for the first 3. The drug was tolerated well.

In conclusion data has been presented which indicates that strontium ranelate maintains its efficacy in relation to vertebral fracture for at least 4 years, and for non-vertebral fractures, for at least 5. There are, in addition, data which suggest that this happens over a longer period (8 years). A *post hoc* analysis with respect to hip fracture carried out after 5 years of treatment indicates results similar to those observed after 3 years. The results of these works while providing valid information with respect to the duration of the effectiveness of the drug, do not change the recommendations of these Guides in this respect, for which reason a recommendation A is retained in relation to vertebral and non-vertebral fractures, and B with respect to hip fractures.

7. Bazedoxifene

Bazedoxifene has been studied in a randomised, double blind, placebo controlled clinical trial[15], which included 6847 postmenopausal women with osteoporosis, assigned 20 or 40 mg/d. of bazedoxifene, 60 mg/d of raloxifene, or a placebo. The primary objective was the appearance of non-vertebral fractures, and changes in BMD and in the makers for bone turnover. With respect to the placebo group, the RR for vertebral fracture for the group treated with bazedoxifene at a dose of 20 mg/d was 0.58 (0.38-0.89); for the group treated with bazedoxifene at a dose of 40 mg/d it was 0.63 (0.42-0.96); and for the group treated with raloxifene, 0.58 (0.35-0.89). None of the three treatments reduced non-vertebral fractures in relation to the placebo, but in a post hoc analysis, bazedoxifene at a dose of 20 mg/d showed an RR in this type of fracture of 0.50 (0.28-0.90) in women with I) BMD in the femoral neck of ≤ 3T, or II) with one or more moderate or serious vertebral fractures, or III) with multiple light fractures.

8. Denosumab

As in the case of zoledronate and PTH 1-84, denosumab was already mentioned in the second version of these guides, but was not considered in the final assessment because the results of its pivotal study had not yet been published nor had it been approved for the market. Its efficacy has been evaluated in the FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) study, whose results have been published recently[16], although the drug is still not yet commercially available. The study consists of a randomised, double blind, placebo controlled clinical trial which involved 7868 women between 60 and 90 years of age with values of BMD of less than -2.5 T in the lumbar spinal column or whole hip. For ethical reasons women who presented with BMD lower than -4.5 T in the aforementioned areas, and those who had previously suffered from one serious, or two moderate fractures, were excluded. The patients were assigned 60 mg. of denosumab, or the placebo, subcutaneously every 6 months for 3 years. The principal objective of the study was the appearance of new vertebral fractures, while the secondary objectives included the appearance of non-vertebral or hip fractures. The study of the following adverse effects was established beforehand: infections, neoplasic processes, hypocalcemia, delay in healing of fractures and osteonecrosis in the jaw bone. The number of women included in the analysis of vertebral fractures was 7393. The RR for new radiographic vertebral fracture was 0.32 (0.26-0.41). The RR for non-vertebral fracture was 0.80 (0.67-0.95) and for the hip, 0.60 (0.37-0.97). The reduction in symptomatic vertebral fractures was similar to that for the radiographic fractures. Not a single example of any of the adverse reactions to denosumab listed above, was observed. Although a higher incidence of eczema (3% vs 1.7%), flatulence (2.2% vs 1.4%) and serious celulitis (0.3% vs one patient [<0.1%]), was noted.

The level of evidence is 1b, with a grade of recommendation of A for the reduction of vertebral and non-vertebral, and hip, fractures.

9. Flouride

Numerous clinical trials have been carried out with fluoride, with disparate results. In 2008 a meta-analysis was published[17] whose conclusion is that fluoride is efficacious in reducing osteoporotic fractures when administered in specific doses. It included 25 studies, and its overall results show an absence of the effect of fluoride on both vertebral and non-vertebral fractures. However, with a daily dose ≤ 20 mg of fluoride (152 mg of monofluorophosphate or 44 mg of sodium fluoride) a significant reduction is observed in both vertebral fractures (OR = 0.3; 0.1-0.9) and non-vertebral fractures (OR = 0.5; 0.3-0.8).

These Guides do not make recommendations on the use of non-approved drugs even for their application as a treatment for osteoporosis.

Osteoporosis in men

We have not found a single work which presents new data on efficacy in the reduction in risk of fracture in male osteoporosis in relation to comments in the second version of the SEIOMM Guides. The refractory study of work on zoledronate[7] included males, but the corresponding results have not been commented on in an independent publication.

By analogy with aledronate and risedronate, and given that there are no reasons to think that the effect of zoledronate should be different in women from in men, SEIOMM includes zoledronate among those drugs recommended for treatment of male osteoporosis. Similar reasons meant that the second version of the Guides recommended the use of teriparatide for osteoporosis in males with high risk of fracture, a recommendation which has subsequently been endorsed by the EMEA.

Steroidal osteoporosis

With reference to osteoporosis related to glucocorticoids, for the production of this update we have included two works, one on teriparatide, and the other on zoledronate.

1. Teriparatide

The efficacy of teriparatide in glucocortisoidal osteoporosis has been studied in a randomised, double blind clinical trial with active control, in which were compared the effect of 20 μg of PTH 1-34/d. with 10 mg of aledronate administered daily over 18 months[19]. It involved 428 men and women from 22 to 89 years of age with osteoporosis who had received glucocorticoids at a dose equivalent to or higher than 5 mg daily of prednisona for at least 3 months. The primary objective consisted of the changes in BMD of the lumbar spinal column. The secondary objectives were changes in BMD for the whole hip, in the markers, in the incidence of fractures and security data. The percentage of patients who experienced a new vertebral fracture in the group assigned PTH 1-34 was 0.6%, and in those assigned aledronate, 6.1% ($p = 0.004$). There were no significant differences in non-vertebral fractures.

A prolongation to 3 years, whose results were presented at the Conference of the ASBMR in 2008, confirmed the significant difference regarding vertebral fractures (1.7% vs 7.7%; $p = 0.007$[20]). It continued without there being significant differences in non vertebral fractures.

The level of evidence in the trial is 1b, and supports the assertion that PTH 1-34 possesses a greater efficacy than aledronate in the reduction of vertebral fractures in patients treated with glucocorticoids (recommendation A).

2. Zoledronate

The efficacy of zoledronate in steroidal osteoporosis has been studied in a non-inferiority trial[21], lasting a year, which compared the effects of zoledronate, administered intravenously at a dose of 5 mg/year, with those of risedronate, administered orally at a dose of 5 mg/day. The population of this study was made up of 383 women who were being treated with 7.5 mg of prednisone. The intervention qualified as "treatment" when the women had been receiving the corticoid for more than three months, and as "prevention" when they had been receiving it for less time. The primary objective it considered were changes in BMD in the lumbar spinal column, and the limit of the margin of non-inferiority was set at -0.7% for the treatment, and at -1.12% for the prevention. The secondary objectives were changes in the apendicular BMD and the incidence of vertebral fractures. All the IC points of the differences for the treatment group (limits 0.67-2.05) and for the prevention group (limits 1.04-2.88) were within the non-inferiority margin. In fact, zoledronate causes increases in BMD significantly greater that zoledronate in the lumbar spinal column, as much in treatment (4.06 ± 0.28% vs 2.71 ± 0.28%; $p < 0.0001$) as in prevention (2.60 ± 0.45% vs 0.64 ± 0.46%; $p < 0.0001$). They were also higher in the femoral neck (1,45 ± 0,31% vs 0,39 ± 0,30%; 1,30 ± 0,45% vs -0·03 ± 0,46%; $p < 0,005$ in both cases). No differences in the incidence of fractures was observed.

The trial has a level of evidence of 1b, and allows a recommendation for the use of zoledronate in glucocorticoidal osteoporosis with a level of recommendation A.

Calcium and vitamin D

During the time which has passed since the editing of the second version of the Guides a diverse number of trials and meta-analyses in relation to the usefulness of both substance in the treatment of osteoporosis have been carried out. However, we do not consider it necessary to consider them in this update, since not one case results in a single change in the recommendations made in these Guides. In the case of these substances is it concluded that "Female patients treated with antiresorptive or anabolics should receive adequate calcium and vitamin D supplements" (recommendation A).

As in the majority of the trials considered in the second version, so in those included in this update calcium and vitamin D was administered both to those patients assigned to the treatment groups, as well as those assigned to the placebo group, which is one of the reasons for recommending its use in patients being treated for osteoporosis.

General conclusion

Since the editing of the current version of the SEIOMM Guides to osteoporosis, a range of works have appeared with information on the efficacy of different drugs in the reduction of the risk of osteoporotic fractures.

Independently of whether these works carry data of interest on the use of the different drugs to which they refer, the Committee charged with producing this update to the Guides considers that the contents of the information referred to only advises the introduction of one change in the algorithm proposed in the current Guides. This change refers to the inclusion of zoledronate.

Zoledronate shares with aledronate and risedronate –the drugs proposed as standard treatment– its efficacy over the three types of fracture: vertebral, non-vertebral, and hip. Its administration, is also very comfortable –once a year– which can facilitate adherence. However, it has some inconvenient aspects, such as its intravenous use and its somewhat higher cost. These reasons have caused us to include zoledronate in the algorithm within the group of standard treatments, although indicating the necessity of assessing with the patient which type of drug is preferable to them. Probably, considering all the aspects together, zoledronate constitutes the alternative, within those drugs of choice, for patients who want to avoid taking drugs orally, or who prefer not to be dependent on taking a drug every week (e.g. polymedicated patients). The committee is aware, however, that its intravenous administration can pose a limit to the use of this drug in those cases in which there is no adequate means available, as can occur in Primary Care Centres.

PTH 1-84 has not demonstrated its efficacy in non-vertebral fractures, and as a consequence the Committee charged with the production of this update found no reason to place it with teriparatide. Its therapeutic characteristics place it, on the contrary, together with the drugs which only reduce vertebral fractures.

Otherwise, although some drugs included in the current algorithm can be seen to have strengthened their position through data provided more recently, this Committee considers that the basic scheme of the aforementioned algorithm should be maintained in its current form, considering the drugs of choice to be aledronate and risedronate, to which is now added zoledronate for occasions when the patient or the doctor thinks that annual intravenous administration of the drug is preferable. In a case in which the doctor thinks that there is an inadequate therapeutic response, or in situations of high risk of fracture (equivalent to the presence of two previous fractures), it is recommended that teriparatide should start to be used, and should continue for 24 months after an antiresorptive (it should be noted that in the previous version it was recommended that the treatment should only last for 18 months, this having been changed by the EMEA). The algorithm indicates that when there are other reasons for not using the standard treatment (poor tolerance, personal preference, etc.), the use of other drugs can be considered, essentially strontium and ibandronate. Finally, in cases in which a female patient has a high risk of fracture of the lower hip (densitometry of the hip above the range for osteoporotics), especially if there is an added risk of breast cancer, one can have recourse to raloxifene.

The recommendation for male osteoporosis remains the same as that in the previous document (aledronate and risedronate as first choice, etidronate and calcitonin as alternatives, and teriparatide in cases of high risk of fracture or of inadequate response), to which is now added zoledronate as a consideration to take into account from the start when the patient or the doctor prefers it.

The scheme for steroidal osteoporosis is much the same: aledronate and risedronate as a first choice, zoledronate also as a first choice if it is considered preferable in the specific circumstances that pertain to the case, and teriparatide if the risk of fracture is high or the response is not thought adequate. The indications for zoledronate and teriparatide did not figure in the earlier document.

Finally, we would like to stress that the application of whichever algorithm should be carried out with flexibility, taking into account the preferences of the patient, the opinions of the doctor and the possibilities of the health system. These factors are especially important when it is necessary to take decisions in respect of drugs which are found at the same level of choice.

Representatives of other Spanish scientific societies who have evaluated the Guides and formulated opinions on them

Luis Aguilera García (Sociedad Española de Medicina de Familia y Comunitaria [SEMFYC]), Javier Ferrer Barriendos (Sociedad Española para el Estudio de la Menopausia [AEEM]), José Filgueira Rubio (Sociedad Española de Medicina Interna [SEMI]), Jordi Fiter Areste (Sociedad Española de Reumatología [SER]), Antonio Herrera Rodríguez (Sociedad Española de Traumatología y Cirugía Ortopédica [SECOT]), Aida Iglesias García (Sociedad Española de Medicina Rural y General [SEMERGEN]), Guillermo Martínez Díaz-Guerra (Sociedad Española de Endocrinología y Nutrición [SEEN]) y Pilar Mesa (Sociedad Española de Geriatría y Gerontología [SEGG]).

ANNEX 1
Committee of Experts of the SEIOMM

Jorge Cannata Andía, Antonio Cano Sánchez, Cristina Carbonell Abella, Manuel Díaz Curiel, J. Bernardino Díaz, López, Adolfo Díez Pérez, Jordi Farrerons Minguela, Alberto García Vadillo, C. Gómez Alonso, J. González Macías, N. Guañabens Gay, Federico Hawkins Carranza, E. Jódar Gimeno, Javier del Pino Montes, Pedro Mezquita Raya, Ana Monegal Brancós, M. Muñoz Torres, Xavier Nogués Solán, José Manuel Olmos Martínez, Pilar Orozco López, L. Pérez Edo, Ramón Pérez Cano, Lluis Pérez Edo, Pilar Peris Bernal, J. Manuel Quesada Gómez, José Antonio Riancho Moral, L. del Río Barquero, Daniel Roig Escofet, Manuel Sosa Henríquez y Antonio Torrijos Eslava.

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