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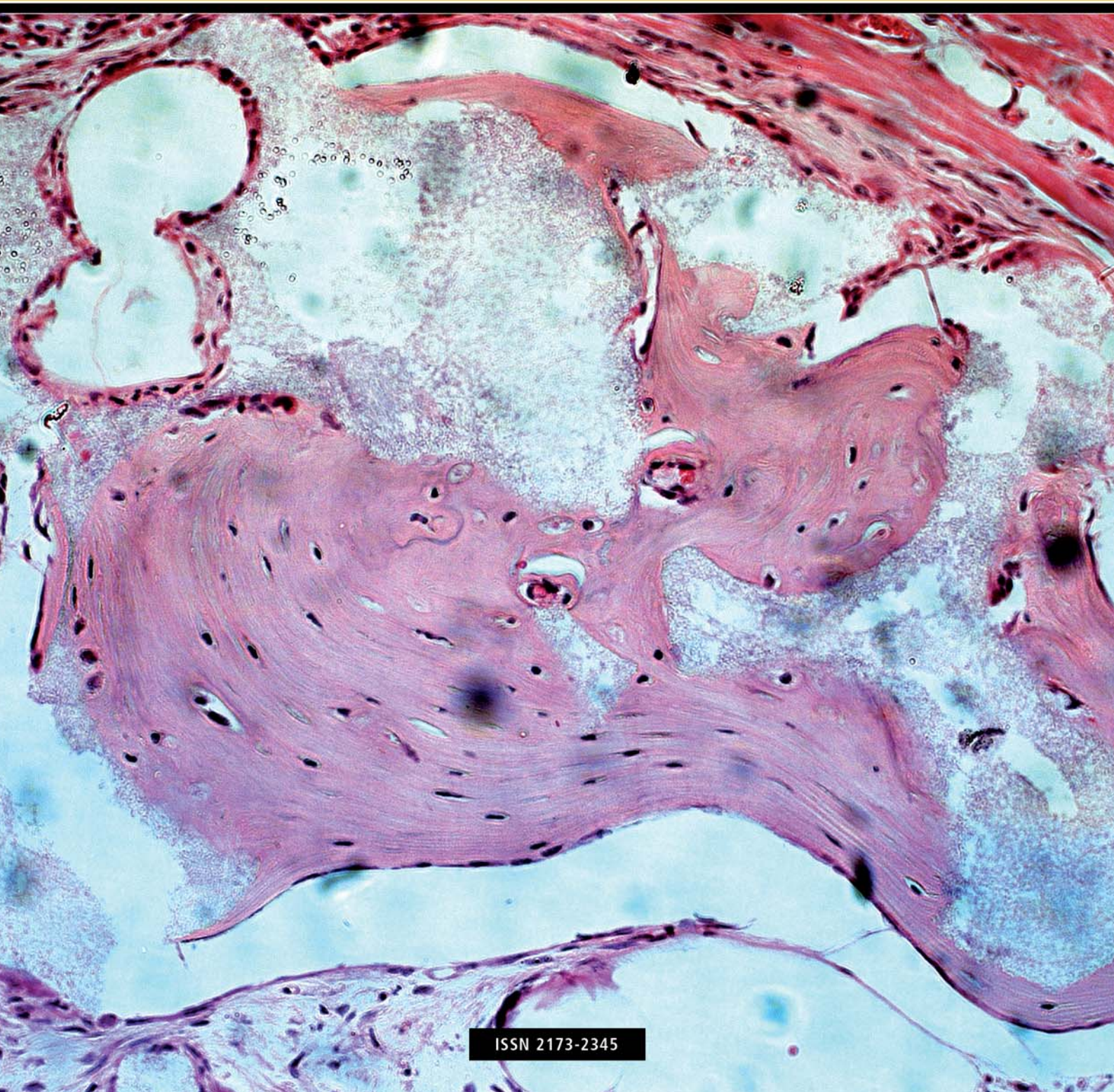

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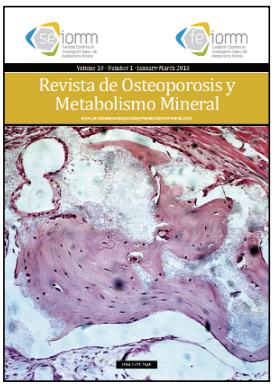

Our cover
Ectopic bone formed by human mesenchymal cells injected into the subcutaneous tissue of immunodeficient mice. The structure of concentric sheets of the bone matrix (stained in pink with H&E staining x 20) and osteocytes inside.

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SUMMARY

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Revista de Osteoporosis y Metabolismo Mineral has recently been acepted for coverage in the Emerging Sources Citation Index, wich is the new edition of the Web of Science that was launched in november 2015. This means that any articles published in the journal will be indexed in the Web of Science at the time of publication.

Editorial Committee

Background history of *Revista de Osteoporosis y Metabolismo Mineral*. The situation ten years on

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As we prepare to mark our journal's 10th anniversary, we would like to retrace our steps along the journey so far and describe the current situation for our readers' knowledge.

The Journal's beginnings and its *raison d'être*

The journal *Revista de Osteoporosis y Metabolismo Mineral (ROMM)* is the scientific publication of the Spanish Society of Bone Research and Mineral Metabolism (SEIOMM, from its original Spanish title). Its creation was agreed on during the XIII SEIOMM Congress held in Oviedo in 2008. Until then, the Society journal was the Spanish Journal of Bone Metabolic Diseases, which had been founded in 1993 by Dr. Aurelio Rapado Errazti and presented at the SEIOMM Congress held in Córdoba, Spain. Known as REEMO, this belonged to the Elsevier publishing company, then Doyma, directed by Dr. Rapado. This journal had an uneven output during its existence. Its best stage was when Dr. Rapado did his utmost to ensure that each issue's content was mostly original material. In its last years, after the sad disappearance of Dr. Rapado, the REEMO decreased both in the number of pages and in the interest that it engendered from the scientific point of view. In 2008, the conditions imposed unilaterally by Doyma-Elsevier on SEIOMM to continue with its cooperation were deemed unacceptable by SEIOMM. In the General Meeting at Oviedo, it was agreed to terminate the current contract with this publisher and create a new publication, owned by the SEIOMM, which is the *ROMM*.

The first point of debate raised at that gathering was whether or not the SEIOMM needed to have a scientific journal. The Assembly agreed, by a considerable majority, to create the current Journal, financed by SEIOMM.

From its inception, *ROMM*'s editorial board established the need to publish a journal with quality articles, editorials and relevant reviews. To this end, standards uniformly accepted by the most prestigious journals, such as those developed in Uniform Requirements for Manuscripts Submitted to Biomedical Journals[1] or the ethical principles on publications: Committee on Publication Ethics (COPE)[2], were accepted from the beginning, including anonymous peer review of the manuscripts submitted, requesting the cooperation of researchers and authors of recognized prestige in the field of bone mineral metabolism. The SEIOMM board of directors at that time, of which we were part director and editor, in its policy of support for the Journal, considered it necessary to establish a strategy for claiming original articles through the research works awarded by the SEIOMM and FEIOMM. This strategy has been maintained by subsequent boards of directors.

The road to wide dissemination. The major databases and repositories

Our first objective was to achieve maximum diffusion and visibility for the Journal. To this end, we have requested its inclusion in all existing databases and repositories. One fact that has facilitated this work has been the completely free nature of the Journal, both to published articles (no amount is charged to authors, whether or not members of the SEIOMM) and to be able to access them through its website[3] in full text and in both languages, Spanish and English, with no embargo period.

In some databases, the lesser ones, our Journal's inclusion was simple, requiring only a request form. In others, an assessment was compulsory by their respective expert committees, a process that sometimes took months, with often varied requi-

rements. The truth is that, once the process started and after the inclusion of the *ROMM* in the first 5 databases, each new acceptance not only increased the number, but acted as a facilitating factor in the following database.

The inclusion in the SciELO database and repository marked the turning point in the publication of the Journal. For this, we had to request it twice, needing to adapt some characteristics and requirements in order to achieve uniformity. The SciELO platform is clearly involved in the DOAJ (Digital Open Access Journals)[4] movement and as a result of this collaboration we have been included in its database, as well as being able to obtain the Digital Object Identifier (DOI) of the articles of our Journal, having jointly signed a collaboration document, published in this same issue, the Declaration of Sant Joan d'Alacant[5].

Currently, the *ROMM* is included in 26 databases and repositories and we have requested inclusion in at least 2 more. Among them, several very important, such as SciELO, Scopus, Web of Science, DOAJ, ERIHPLUS and Google Scholar. The inclusion in Scopus will make it possible to attain an impact factor for the first time, although it will be facilitated by Elsevier in the form of Cite Score and Scimago Journal Rank (Figure 1).

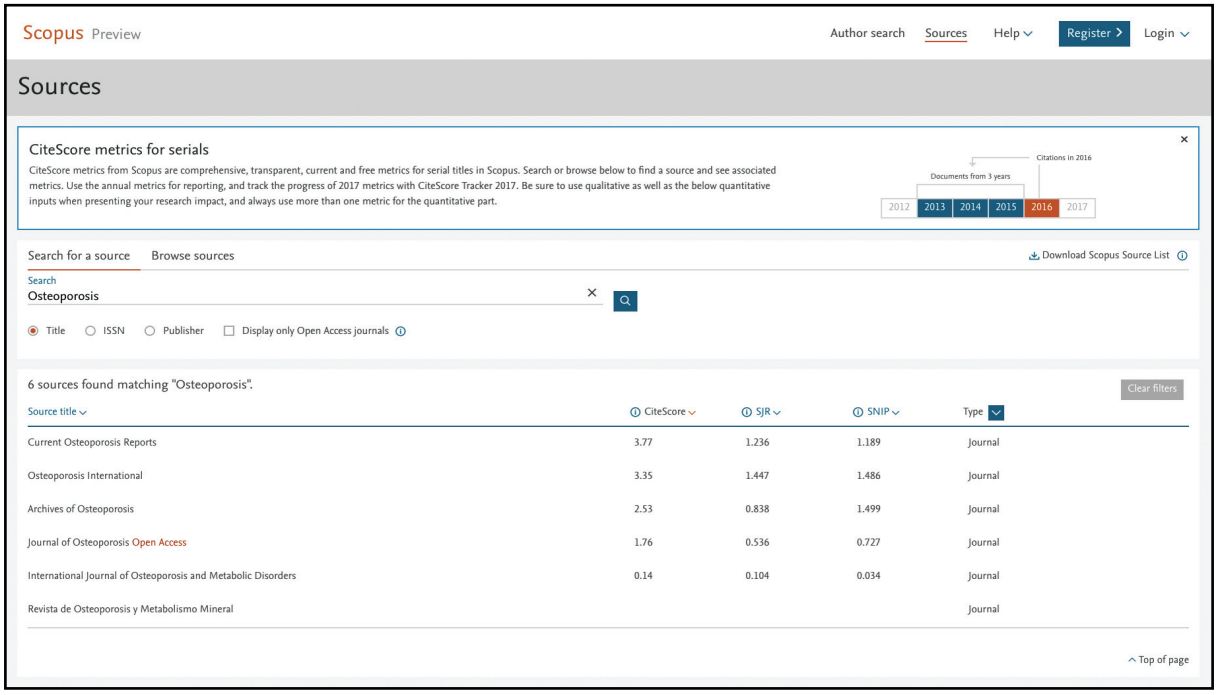
Having a presence in virtually all databases, with the exception of Medline, we have some objective and external data that inform our publication's quality. Thus, in 2015, the "H index" (system proposed by Jorge Hirsch, of the University of California, to measure researchers' professional quality) of the Spanish scientific journals according to Google Scholar or Academic was published. Over the period of 2010-2014, the *ROMM* attained a ranking of 63[6] with an index H of 7 and a median H of 9. The same authors repeated the study including the year 2015, then observed a decrease of the *ROMM* to position 87, with the same values of index H and of its median[7]. Given that the H index is calculated based on the distribution of the citations received by a researcher's scientific works, we conclude that the main problem the *ROMM* now has is that its articles are rarely cited, even by its own authors[8].

However, analyzing other bibliometric indexes that assess the quality of journals, regardless of the number of citations of their articles, the University of Barcelona has developed an application called Information Matrix for the Analysis of Journals (MIAR). Based on different data, it calculates each year the ICDS (Composite Index of Secondary Diffusion), which is an indicator that shows the visibility of a journal in different scientific databases of international scope, or, failing that, in evaluation repertoires of periodicals[9]. An elevated ICDS means that the journal is present in different sources of information of international relevance. In its latest update, of 2018, the *ROMM* obtained an ICDS of 9.5 points, out of a possible maximum of 11, having increased this index year after year, as in 2016 it was 9.3 and in 2017, 9.4[10]. Table 1 shows some ICDS from journals related to bone mineral metabolism, for comparison.

The future of the *ROMM*: Where are we going? Is there life beyond Medline?

The main objective of *ROMM*'s management and editorial team and SEIOMM's board of directors is its inclusion in the Medline database. In the last 5 years, we have twice requested its expert commit-

Figure 1. Journal of Osteoporosis and Mineral Metabolism: its presence in Scopus



tee's evaluation, having obtained in 2014 a score of 2.5 and in 2017, 2.7 points, with 3 points being necessary on a maximum of 5 to pass the cut-off threshold and be included. We have carefully analyzed the report (which was presented at the SEIOMM Assembly last October) and we are working to correct everything that can be improved to try again as soon as possible, which will be from May 2019. One of the aspects that we have worked on lately is to improve the Journal web page and adapt it to the editing formats required by some databases. Profound changes in the computer program were carried out.

Another aspect that we must improve is the H index in Google Scholar and the Cite Score in Scopus. To attain this, the articles published in the *ROMM* must be cited in other journals, preferably those that are indexed in the Journal of Citation Reports, in other words, those that have an impact factor. To encourage the authors and achieve this goal, the current SEIOMM board of directors, in agreement with the journal's editorial team, has established the "Support to the SEIOMM Magazine" award sponsored by Rubió Laboratories[11].

Now, what would happen if the inclusion of the *ROMM* in Medline was delayed for a few years? This scenario, although undesirable, is possible. The criteria applied by the Medline Committee of Experts are sometimes difficult to understand and therefore correct. In our opinion, the *ROMM* is already included in multiple databases and repositories that ensure its visibility. On the other hand, we also have an external recognition with objective data on its quality[6-10]. However, the inclusion in Medline is still one of our goals and we will strive to achieve it.

As a conclusion, the SEIOMM has a Contrast Quality Journal that in a relatively short period of time has been widely disseminated (especially in the countries of Central and South America), but which requires the collaboration and involvement of researchers, and in a very special way those that are associated with the SEIOMM, because it is their Journal, which must be materialized by submitting quality articles and citing the Journal's contents in other scientific publications with an impact factor.

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Table 1. ICDS of some journals in 2017, according to MIAR [9,10]

Journal	ICDS
Journal of Bone and Mineral Research	11
Bone	11
Calcified Tissue International	11
Osteoporosis International	10.9
Journal of Clinical Densitometry	10.8
Current Osteoporosis Reports	10.7
Archives of Osteoporosis	10.6
Revista de Osteoporosis y Metabolismo Mineral	9.5
Journal of Osteoporosis	9.4
International Journal of Osteoporosis and Metabolic Disorders	7.5
Endocrinología y Nutrición	4.5

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Vitamin D deficiency in postmenopausal Ecuadorian women with diabetes mellitus type 2

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Summary

Objectives: To know the prevalence of vitamin D insufficiency in Ecuadorian postmenopausal women with type 2 diabetes mellitus, and to investigate the correlation between serum levels of vitamin D, variables of metabolic control of type 2 diabetes mellitus, markers of bone metabolism and bone mineral density.

Design, materials and methods: Epidemiological study descriptive and cross-sectional design, carried out between January 2012 November 2015. In 124 postmenopausal women, 96 with type 2 diabetes mellitus and 28 without diabetes, we measured serum levels of vitamin D, glycosylated hemoglobin, HOMA-IR, parathyroid hormone, ionic calcium, osteocalcin, urinary deoxypiridinoline and bone density. Premenopausal women, kidney disease, type 1 diabetes, secondary osteoporosis, and those who received treatments that affect bone metabolism, were excluded.

We separate patients with type 2 diabetes mellitus in 2 groups: group sufficiency vitamin D (>30 ng/mL) and group insufficiency vitamin D (<30 ng/mL). The latter group was subdivided into insufficiency (<30 ng/mL), deficiency (<20 ng/mL) and severe deficiency (<10 ng/mL). An analysis of linear correlation between vitamin D and all variables was performed.

Results: We found a significant reduction in serum levels of vitamin D in patients with type 2 diabetes mellitus compared with the controls (p<0,034). The group of patients with diabetes mellitus had the following characteristics: age, 66 (13) years; body mass index, 28.5 (6.5); vitamin D, 20.9 (8.2) ng/mL; and parathyroid hormone, 34 (21) pg/mL; 12.5% had sufficiency and 87.5% insufficiency of vitamin D; among these, 44 had insufficiency, 36 deficiency and 4 severe deficiency. There is a significant correlation between VD, age (p=0,036) and lumbar bone density (p=0,031). We found no correlation between vitamin D and the variables of metabolic control of diabetes.

Conclusions: We found a high prevalence of vitamin D insufficiency in the Ecuadorian postmenopausal women with type 2 diabetes mellitus.

Key words: *diabetes, hypovitaminosis D, parathyroid, densitometry, postmenopausal, prevalence..*

Introduction

Type 2 diabetes mellitus (T2DM) is a worldwide epidemic. The International Diabetes Federation (IDF) predicts that the current figure of 415 million patients affected with diabetes will increase to 642 million by 2040[1]. In Ecuador, the prevalence of T2DM in the age-adjusted population is 9.2%, according to 2015 IDF estimates[1].

Vitamin D deficiency has been linked to a wide range of health problems, including various cancers and autoimmune or metabolic diseases, such as type 1 diabetes mellitus and T2DM[2].

Current studies confirm that the prevalence of vitamin D deficiency in the general world population is actually as high as 50-80%[3], even occurring in countries located in geographical areas which receive sunshine year-round.

Although the high prevalence of hypovitaminosis D has been considered a serious public health problem in Latin America and the Caribbean, the precise extent of the problem is not known due to the lack of information in the general population[4].

Previous studies have described a high rate of vitamin D deficiency in the general population[5]. However, few have reported the status of vitamin D in patients with T2DM. The prevalence of vitamin D deficiency or insufficiency in patients with T2DM varies from 70 to 90%[6-8], depending on the threshold used to define vitamin D deficiency or insufficiency.

In Ecuador, the status of serum vitamin D levels in the general population has recently been described[9], but not in patients with T2DM. This study was conducted to determine the prevalence of vitamin D insufficiency in Ecuadorian postmenopausal women with T2DM and to investigate whether there is a correlation between serum levels of vitamin D, markers of bone metabolism, bone density, and metabolic control variables of T2DM.

Material and methods

Population group and study design: a descriptive and cross-sectional epidemiological study was carried out to determine the prevalence of hypovitaminosis D in the period from January 2012 to November 2015 at the Teaching Hospital of the Guayaquil National Police Nº 2 (HDPN-G2).

The city of Guayaquil, located on the Pacific coast (2º11'00"S), encompassing an area of 345 km^2, is the most populated city in Ecuador. According to the most recent (2010) Census of Population and Housing data, provided by the National Institute of Statistics and Censuses of Ecuador, Guayaquil has 16% of the country's total population[10].

The study protocol was approved by the HDPN-G2 Ethics and Research Committee. All patients signed informed consent before participating in the study.

The study included 2 groups of postmenopausal women residing in Guayaquil. One group included those who were undergoing their T2DM check-up in the endocrinology office. The other group was comprised of those who attended for a routine review for non-diabetes related medical problems in the Internal Medicine practice of HDPN-G2 (control group: Non T2DM). Serum levels of 25(OH) were measured as well as total vitamin D (including D3+D2), glycosylated hemoglobin (HbA1c), parathyroid hormone (PTH), ionic calcium in 96 postmenopausal women with type 2 diabetes mellitus and in 28 non-DM2 controls, osteocalcin, and deoxypyridinoline in urine. We also conducted basic biochemistry tests in serum: creatinine, complete blood count, fasting blood glucose, liver enzymes, serum lipids, and proteinogram.

Premenopausal patients with a history of ketoacidosis, type 1 diabetes mellitus and nephropathy, and those receiving medications that affect bone metabolism (bisphosphonates, estrogens, calcium, anabolic steroids or other male or female hormones) were excluded.

Diagnosis of type 2 diabetes

We followed the international criteria for diagnosing T2DM[11], which considers the disease to be present if at least one of the following criteria are met: (1) FPG (fasting plasma glucose) ≥126 mg/dL; (2) HbA1 ≥6.5%. Patients with T2DM received various combinations of treatments for their metabolic control: metformin, insulin, DPP4 inhibitors, and diet. The duration of T2DM was established based on the dates recorded in the patient's clinical history and/or self-referral.

Classification of vitamin D levels

Normal values of serum vitamin D are defined as those from 30 to 76 ng/mL[2]. Patients were divided into 2 groups according to the serum vitamin D level: sufficiency group (≥30 ng/mL) and failure group (<30 ng/mL)[5].

The latter group was divided into 3 subgroups: insufficiency (<30 ng/mL), deficiency (<20 ng/mL) and severe deficiency (<10 ng/mL)[6].

Serum ionic calcium was measured after 12 hours of fasting and without tourniquet, under anaerobic conditions, by direct measurement with selective ion electrode (NOVA-8 equipment), with reference values 4.5-5.6 mg/dL.

Parathyroid hormone PTH (intact molecule) was measured with SIEMENS Immulite 2000 (enzyme-labeled two-site solid-phase chemiluminescent immunometric assay), whose reference value is 12-72 pg/mL. The intra-assay precision performance had a coefficient of variation of 5.7, 4 and 4.2% for concentrations of 72, 258 and 662 pg/mL, respectively, and an inter-assay coefficient of variation of 6.3 and 8.8% for 54 and 387 pg/mL concentrations, respectively. The limit of detection is 3.0 pg/mL and a linearity up to 500,000 pg/mL without Hook effect.

Serum level of total 25(OH) vitamin D (D3+D2) was measured by chemiluminescence, with reference values 30-70 ng/mL (Centauro kit; competitive 1-step assay with fluoroscein-marked anti-

body). Total precision performance had a coefficient of variation of 11.1, 9.6, 9.8, 8.2, 7.8, 4.8% for concentrations of 11.7, 18.0, 32.4, 49.9, 55.8, 132.1 ng/mL respectively, a detection limit of 3.2 ng/mL and a linearity up to 150 ng/mL. Renal function integrity was recorded in all cases by measuring serum creatinine levels and calculating endogenous creatinine clearance expressed in ml/ml (formula corrected for age, sex, weight and serum creatinine):

[(140 – age in years) x weight (kg)] / [(72 x serum creatinine (mg/dL) and in women x correction factor 0.85].

Glycosylated hemoglobin in EDTA whole blood was measured by HPLC assay (diagnostic value, >6.5%). Osteocalcin, by electrochemiluminescence, ROCHE MODULAR E-170 (reference values for postmenopausal women: 20-48 ng/mL). Deoxypyridinoline (DPD) in urine, by chemiluminescence, whose total precision performance shows a coefficient of variation of 12.0, 11.0, 7.1, 6.3 and 4.3% for concentrations of 25, 32, 78, 120 and 275 nM, respectively (reference values: 3-7.4 nM DPD/mM creatinine).

Bone mineral density (BMD) in the lumbar spine (L2-L4) and femoral neck were determined by dual energy X-ray absorptiometry (DXA: Hologic Discovery), and the data were expressed as T-score units. As no reference values were available for the Ecuadorian population, the NHANES North American reference values were used.

Data analysis

Data on demographic and biochemical variables are expressed as median and interquartile range. To compare the clinical and biochemical characteristics between groups, the Wilcoxon signed-rank test was used. A linear correlation analysis (Spearman's coefficient) between vitamin D and all other variables was performed. Statistical significance was considered with values of $p<0.05$. The prevalence of hypovitaminosis D was calculated as the number of existing cases divided by the total population screened and expressed as a proportion of every 100 adults. All analyzes were carried out using Epidata software version 4.2. The confidence intervals of the Spearman correlation coefficient were calculated using the Stata software version 14.2 (2016).

Results

Demographics of cases and controls

There were no differences between the two groups (T2DM versus non- T2DM) in terms of age, body mass index (BMI), intact PTH, osteocalcin, urinary deoxypyridinoline, and BMD in the lumbar region or femur. The groups presented significant differences in the variables of metabolic control: the HOMA-IR index ($p=0.002$) and glycosylated hemoglobin ($p<0.001$). Serum vitamin D levels were significantly lower ($p<0.034$) in the T2DM group.

Demographic data and characteristics of cases and controls are presented in table 1.

Severity and extent of vitamin D deficiency

In the T2DM group we found a significant reduction in serum vitamin D levels: 12.5% (95% CI=5.3-19.6) of the cases had vitamin D sufficiency (n=12) and 87.5% (95% CI=80.3-94.6) had vitamin D insufficiency (n=84), of which 52% (95% CI=51.1-63.6) (n=44) had insufficiency; 42% (95% CI=31.7-54) (n=36), moderate deficiency and 4.8% (95% CI=1.3-11.7) (n=4) severe deficiency. In the non-T2DM group, 67.8% (95% CI=48.8-87) (n=19) had vitamin D sufficiency and 33% (95% CI=13-51) (n=9) had insufficient vitamin D. Figure 1 shows the frequency distribution of vitamin D levels in postmenopausal women with DM2.

There were no differences in the T2DM group between subgroups of patients with adequacy and that of patients with vitamin D insufficiency in terms of age, BMI, HbA1c, PTH, ionic calcium, osteocalcin, urinary deoxypyridinoline, or bone mineral density. The subgroup with vitamin D insufficiency presented a higher HOMA-IR than that with sufficiency, although it did not reach statistical significance ($p=0.093$). Table 2 shows the demographic data, metabolic variables, bone density and vitamin D status in patients with T2DM.

Correlation between vitamin D, markers of bone metabolism and variables of metabolic control of T2DM

We found a slight but significant correlation between vitamin D and age ($r=-0.21$, $p=0.03$) but not with BMI and the metabolic control variables of T2DM (glycosylated hemoglobin, HOMA-IR index), nor with markers of bone remodeling (PTH, ionic calcium, osteocalcin, deoxypyridinoline). There is a slight ($r=0.22$) but significant correlation between vitamin D and bone density in the lumbar region ($p=0.03$), but not with femoral neck BMD. Table 3 shows the correlation coefficients between vitamin D, markers of bone metabolism and metabolic control variables of DM2.

Discussion

The high incidence of T2DM worldwide[1] and the accumulated evidence on the status of vitamin D under different conditions[2] make it extremely important to determine the relationship between vitamin D and diabetes mellitus.

To our knowledge, this is the first study conducted in Latin America, which establishes the prevalence of hypovitaminosis D in postmenopausal women with T2DM.

Hypovitaminosis D appears to be a prevalent phenomenon in populations around the world, in which they influence the type of ethnicity, sex, body mass index, traditional dress, nutrition, consumption of vitamin supplements and level of urbanization[5].

Most epidemiological information on hypovitaminosis D in the world population comes from studies in Europe, the Middle East, India, and Asia[3,5], with few studies in our region[4,9].

Choosing the cut-off point to define vitamin D deficiency in the population remains a controver-

sial issue. Some consider levels >30 ng/mL to define sufficiency, while others set adequate levels of 20 ng/mL. According to the definition of the Endocrine Society (USA), vitamin D values below 20 ng/mL are considered deficient, and values between 21 and 29 ng/mL are insufficient[2]. According to these cut-off points, it is estimated that 20 to 100% of elderly men and women have vitamin D deficiency in the United States, Canada and Europe[13].

In 3 studies conducted in Latin America, a cutoff point of <20 ng/mL[14-16]; and in another <20 and <30 ng/mL for deficiency and insufficiency, respectively[9].

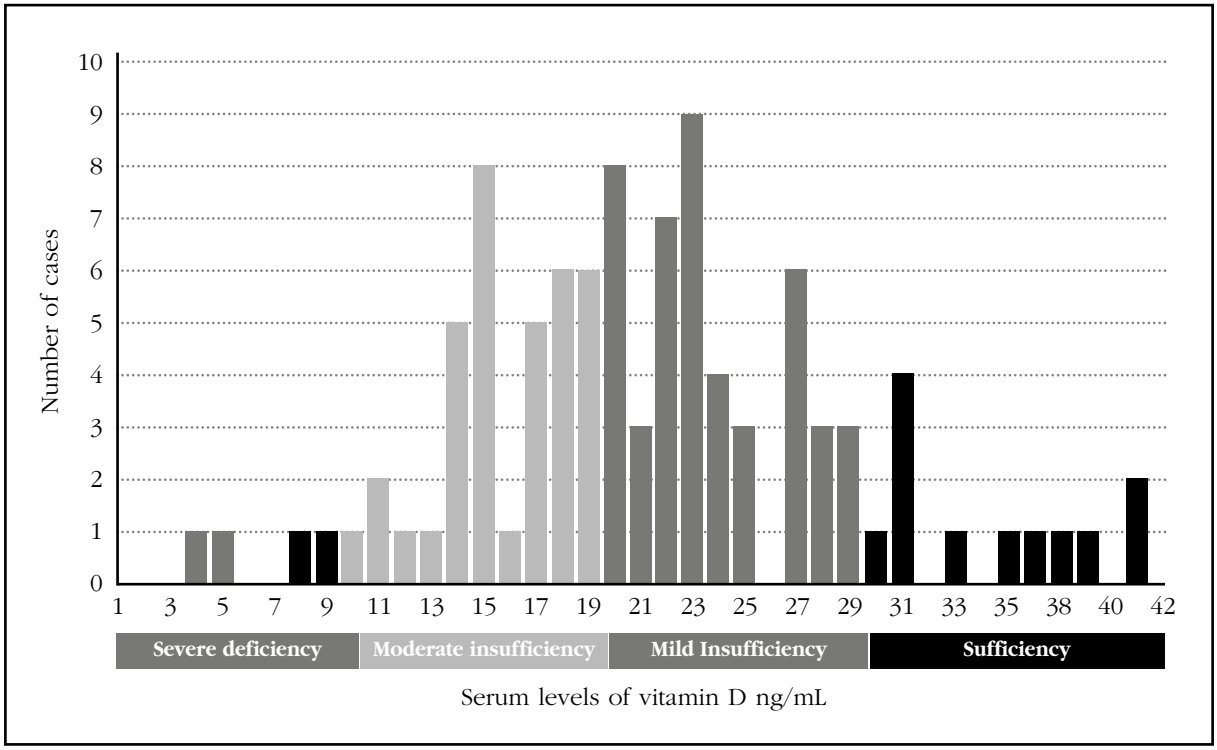
With a cutoff <20 ng/mL, the prevalence of vitamin D deficiency among women in Santiago de Chile is 60%[14]. In Argentina, the prevalence of vitamin D deficiency varies from 73% in southern cities to 50% in northern cities[15], and in Brazil it is 17%, much lower than in previous series[16].

Table 1. Demographic data and characteristics of the 2 study groups

	T2DM n=96	No T2DM n=28	p
Age (years)	66 (13)	65 (15.5)	0.569
Body mass index (kg/m^2)	28.5 (6.5)	28.4 (1.8)	0.909
HOMA-IR	4.22 (5.7)	3 (2.3)	0.002*
Glycosylated hemoglobin (%)	6.4 (2.2)	5.8 (0.6)	0.0001*
Vitamin D (ng/mL)	20.9 (8.1)	25.18 (12.3)	0.034*
PTH intact (pg/mL)	34 (21.5)	36 (30.7)	0.445
Ionic calcium (mg/dL)	4.9 (0.32)	4.91 (0.21)	0.792
Osteocalcin (ng/mL)	15.34 (10.26)	15.34 (10.3)	0.171
Deoxypyridinoline (nM DPD/mM Cr)	6.5 (2.7)	5.5 (3.07)	0.28
Lumbar spine BMD (T-score)	-1.5 (2.2)	-1.4 (1.8)	0.971
BMD femoral neck (T-score)	-1.5 (1.5)	-1.4 (2.2)	0.692

*p<0.05 (Wilcoxon Signal Range Test). Data are expressed as medians and interquartile range. T2DM: type 2 diabetes mellitus; HOMA-IR: Homeostasis Model of Assessment-Insulin Resistance Index; PTH: parathyroid hormone; BMD: bone mineral density.

Figure 1. Distribution of vitamin D frequency frequencies in postmenopausal women with T2DM



In Ecuador, a recent study[9] in the elderly population has described a prevalence of vitamin D insufficiency and deficiency of 68 and 22%, respectively. Despite the abundant natural light throughout the year, this condition varies considerably among the different regions and zones of our country. It is more frequent in older women, the inhabitants of the Andean region and the indigenous race[9].

The prevalence of vitamin D deficiency or insufficiency in patients with T2DM also depends on the threshold used to define it. In our study, vitamin D insufficiency was defined as a vitamin D level <30 ng/mL, which is in accordance with the recommendation of the International Osteoporosis Foundation[5,17].

In general, the prevalence of hypovitaminosis D in patients with T2DM reported in international series is high. In a previously published study, 74.6% of patients with T2DM had D hypovitaminosis[8]. In another, prevalence (cutoff <20 ng/mL) was more frequent in diabetics compared to controls (83% vs 70%, p=0.07)[7]. In a more recent study, prevalence was greater in diabetic patients than in control subjects (90% vs 83%, p<0.01)[18]. Data on hypovitaminosis D in patients with T2DM are not available in Latin America.

Table 2. Demographic data, metabolic variables, bone density and vitamin D status in patients with T2DM

	Sufficiency VD (n=12)	Insufficiency VD (n=84)	p
Age (years)	61 (22.5)	66 (11.5)	0.272
Body mass index (kg/m^2)	26.97 (10.7)	28.69 (5.8)	0.720
HOMA-IR	3.26 (6.7)	4.28 (5.1)	0.093
Glycosylated hemoglobin (%)	7.25 (3.5)	6.4 (2.3)	0.284
Vitamin D (ng/mL)	34.59 (7.1)	20.23 (7.4)	0.002*
PTH intact (pg/mL)	34.5 (20.5)	34 (23)	0.583
Ionic calcium (mg/dL)	4.98 (0.25)	4.9 (0.32)	0.410
Osteocalcin (ng/mL)	13.99 (10.7)	15.3 (10.3)	0.480
Deoxypyridinoline (nM DPD/mM Cr)	6.35 (4.02)	6.56 (2.67)	0.646
BMD lumbar spine (T-score)	-1.40 (2.8)	-1.50 (2.23)	0.724
BMD femoral neck (T-score)	-1.00 (2.85)	-1.50 (1.40)	0.875

*p<0.05 (Wilcoxon Signal Range Test). Data are expressed as medians and interquartile range. T2DM: type 2 diabetes mellitus; HOMA-IR: Homeostasis Model of Assessment-Insulin Resistance Index; PTH: parathyroid hormone; BMD: bone mineral density.

Table 3. Correlation between vitamin D, markers of bone metabolism and variables of metabolic control of DM2

	r	IC 95%	p
Age (years)	-0.215	-0.4 a -0.015	0.036*
Body mass index (kg/m^2)	-0.113	-0.313 a 0.098	0.294
HOMA-IR	0.097	-0.124 a 0.309	0.388
Glycosylated hemoglobin (%)	-0.024	-0.245 a 0.200	0.838
Ionic calcium	-0.042	-0.245 a 0.156	0.654
PTH intact (pg/mL)	0.18	-0.021 a 0.368	0.079
Osteocalcin (ng/mL)	-0.052	-0.25 a 0.15	0.617
Deoxypyridinoline (nM DPD/mM Cr)	-0.149	-0.353 a 0.069	0.179
BMD lumbar spine (T-score)	0.221	0.021 a 0.404	0.031*
BMD femoral neck (T-score)	0.155	-0.047 a 0.345	0.131

*p<0.05; r: Spearman correlation coefficient; 95% CI: 95% confidence interval; T2DM: type 2 diabetes mellitus; HOMA-IR: Homeostasis Model of Assessment-Insulin Resistance Index; PTH: parathyroid hormone; BMD: bone mineral density.

The results of the present study are similar to those of recent studies in non-Latin American populations, which demonstrated a high prevalence of hypovitaminosis D in patients with T2DM[6,19-21].

It is unclear whether vitamin D deficiency and poor glycemic control are causally related or represent two independent features of T2DM. Previous studies have reported inconclusive results regarding the association between vitamin D status and HbA1c[22]. In our study, vitamin D-deficient women had lower levels of HbA1c compared to those who had sufficiency, although this did not reach statistical significance. This adds to the evidence that the vitamin D status is not associated with the metabolic control variable HbA1c.

An inverse association has been reported between serum vitamin D levels and BMI >30, and therefore, obesity would be associated with vitamin D deficiency[23]. In postmenopausal women with T2DM, obesity is also considered a risk factor for vitamin D deficiency[20]. However, our data do not confirm previous reports of a negative association between vitamin D and BMI. In contrast, in our sample cases and controls were not different in their BMI, although both groups were overweight.

The main finding of this cross-sectional study is the high prevalence (85.7%) of vitamin D insufficiency (<30 ng/mL) in patients with T2DM, with an average vitamin D level of 22 ng/mL. However, this value is higher than the average vitamin D reported for patients with diabetes and obesity in other series in Africa and Asia (16 to 17 ng/mL)[24,25] and similar to a sample of patients in the United States (23 ng/mL)[26].

In Ecuador, there is no definite four-season separation as in the northern and southern hemispheres. The city of Guayaquil, where this study was conducted, is located on the coast of the Pacific (2°11'00"S), and its inhabitants enjoy open skies, warm weather and sunlight throughout the year, their garments of clothing are light and expose much of their skin.

The results of this study contradict the assumption that abundant exposure to sunlight throughout the year reduces the risk of hypovitaminosis D. The discrepancy between our results and outcomes in other ethnic groups may reflect racial differences, lifestyle factors (physical inactivity, limited sun exposure) and/or insufficient intake of vitamin D, or all.

Vitamin D deficiency is associated with an increased risk of fracture[27], and is associated with diffuse muscular pain, muscle weakness and increased risk of falls[28,29]. However, despite the increased risk of fracture, bone mineral density is generally higher in patients with T2DM[30]. In our study, we did not investigate the prevalence of fragility fractures, so we cannot confirm this evidence.

Previous studies indicate that even a slight reduction in serum vitamin D levels may be associated with secondary hyperparathyroidism, increased remodeling, and accelerated bone loss, which increase the risk of bone fractures[31]. In the present study, intact PTH and ionic calcium levels were within the normal range, so our results do not confirm the association between vitamin D, PTH and calcium that has been described in the literature.

There are some strengths and limitations related to the present study. Although the sample of population was relatively small, we were able to compare it with a control group, which allows us to establish inferences with the general population.

The present study does not provide data that could explain the higher prevalence of hypovitaminosis D in patients with T2DM.

It is generally accepted that vitamin D levels vary with daily activity and exercise level. In our study we do not consider these variables, and although in our country we only have one dry season and one rainy season, we do not know if in our population the measured variables are modified with the time of year.

The prevalence of hypovitaminosis D in the general population has been overestimated due to improper use of a high cut-off point for vitamin D. Geographic latitude with a large amount of sunlight exposure or low calcium consumption[9], which generally occurs in Ecuador, will undoubtedly affect the cut-off point for the development of vitamin D deficiency. In this sense, the cut-off point chosen to define vitamin D insufficiency may not be adequate for our predominantly mestizo population, using the one for predominantly Caucasian populations, as these values vary widely even from region to region[12].

Considering that in this sample the average vitamin D was very close to 20 ng/mL, further studies are required to evaluate the adequacy of the vitamin D cutoff points chosen in Ecuadorian women with T2DM. In this study, a lower cutoff point for vitamin D normality would undoubtedly have resulted in a much lower prevalence of hypovitaminosis D.

Despite these limitations, the present study is the first to report the prevalence of vitamin D insufficiency among Ecuadorian postmenopausal women with T2DM, and allows us to infer that this prevalence is higher in patients with T2DM than in the population without T2DM.

In conclusion, our study found that vitamin D deficiency was significantly more frequent among Ecuadorian postmenopausal women with T2DM compared to those without T2DM.

Our data indicate that the availability of abundant sunlight is not sufficient for the prevention of vitamin D deficiency. This warns us of the risk of hypovitaminosis D in the diabetic population, regardless of geographical location.

The high prevalence of hypovitaminosis D in postmenopausal women with T2DM highlights the need for prospective studies to evaluate the impact of vitamin D supplementation on glucose metabolism. Additional studies should clarify the relationship between hypovitaminosis D and osteoporosis in patients with T2DM.

The results of our study may help the country's public health authorities implement vitamin D supplementation policies, especially among the population at risk of this condition.

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Relationship between the presence of anemia and the risk of osteoporosis in women with rheumatoid arthritis

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Summary

Introduction: Patients with rheumatoid arthritis present a high prevalence of osteoporosis, partly due to the use of glucocorticoids. However, there are other causal factors.

Material and methods: 122 women diagnosed with rheumatoid arthritis were studied. Serum hemoglobin concentrations were determined and bone densitometry carried out by dual energy X-ray absorptiometry. A multivariate logistic regression model was used to determine the association of the variables studied.

Results: 32.8% of the women studied presented hemoglobin <12 g/dL. The mean T-score in the lumbar spine was -1.8±1.5; 36.9% had a low bone mass, 32.8% osteoporosis criteria and 30.3% normal T-score. The mean of the femur T-score was -0.6±1.4; 63.9% was normal value, 23.8% presented low bone mass and 12.3% criterion of osteoporosis. Hemoglobin ≥12 g/dL and a bone mineral density (BMD) of the normal femur (p=0.003), and between hemoglobin <12 g/dL and BMD of femur with osteoporosis (p<0.000). There was an independent association between osteoporosis and body mass index <30 kg/m^2 (OR=4.1, 95% CI: 1.4-11.4, p=0.009) and the presence of anemia (OR=8.9, 95% CI: 3.7-22.4, p=0.001).

Conclusions: In our study, we observed an association between anemia and low bone mineral density in women with RA mainly in the region femoral, which indicates that adequate and timely management of anemia is important in these patients.

Key words: *anemia, osteoporosis, rheumatoid arthritis.*

Introduction

Patients with rheumatoid arthritis (RA), may suffer anemia associated with a chronic ailment, which tends to be normocytic, normochromic or, less frequently, microcytic, aregenerative with normal transferrin serum levels[1]. Given the lack of effective treatment, anemia is very prevalent. It may range from 30 to 70%, according to different reported series[2].

Among the mechanisms involved in the development of anemia is the shortening of the useful life of erythrocytes, inadequate erythropoiesis, abnormalities in iron metabolism, as well as the inflammatory effect of cytokines, with interleukin-6 affecting hepcidin, a hormone that plays a significant role in the development of anemia in patients with RA. By decreasing iron levels, it regulates the transport of iron through the membranes and inhibits its intestinal absorption and release of iron, macrophages and hepatocytes[1].

Patients with RA usually have a higher risk of developing osteoporosis than the general population, increasing the risk of fractures and morbidity. The incidence is usually around 12-20% in the hip and spine[3].

Osteoporosis in patients with RA may be due to chronic inflammation, the activation and inhibition of bone cell function, modified body composition, the use of glucocorticoids, diet, low levels of physical activity and to the presence of anemia[4,5].

Researchers have linked the presence of anemia with osteoporosis. Excess effort of the hematopoietic system secondary to constant blood cell production in patients with anemia plays a major role in osteoporotic development. In support of this idea, hematological diseases that present chronic anemia (as in the case of beta thalassemia major, sickle cell anemia, chronic hemolytic anemia, pernicious anemia and hemophilia) have been found to concomitantly show osteoporosis[5].

A study in murine models reported that chronic blood loss produced an increase in the hematopoietic microenvironment, relatively reducing the amount of bone generated and activating its resorption process[6].

We carried out our study to determine the factors associated with osteoporosis of the femur (OF) and particularly, if the low levels of Hb (Hb <12 g/dL) are associated with OF in a female population with RA.

Material and methods

A descriptive, observational, retrospective study was carried out, in which patients older than 18 years were included with the diagnosis of RA, according to the ACR/EULAR 2010 criteria, that attended our Rheumatology outpatient service during the period of January to June 2016. Clinical records were reviewed and age, gender, history of diabetes mellitus, systemic arterial hypertension and smoking were recorded as variables; as well as factors associated with RA, such as the duration of the disease and the use of glucocorticoids or disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, leflunomide, azathioprine; no patient received biological treatment. Anthropometric variables were also measured. The participation in the study was authorized by each patient signing an informed consent.

Measurement of anthropometric variables

The patients were weighed with a scale, previously calibrated, barefoot and with light clothing, expressing the results in kilograms. The height was measured by means of a standard height rod with the patient standing, expressing the results in meters. With these results, the body mass index (BMI) was calculated by means of the weight/height^2 formula (kg/m^2), classifying the results in the low weight ranges: <18.5 kg/m^2; normal: 18.5-24.9 kg/m^2; overweight: 25-29.9 kg/m^2; obesity: >30 kg/m^2.

Determination of biochemical parameters

With a minimum fast of 8 hours, serum albumin concentrations were determined (considering as hypoalbuminemia <4 g/dL), ultrasensitive C-reactive protein (CRP-Us, considering as a cut-off value ≥2 mg/dL due to its association with cardiovascular risk); and hemoglobin (Hb) <12 g/dL as anemia, since it is the cut-off point set by the World Health Organization (WHO) for non-pregnant women[7]. The positive rheumatoid factor (RF) was considered with values above 15 IU/mL. Anti-citrullinated cyclic peptide (APCC) antibody values >5 IU/mL were considered positive.

Disease activity

Disease activity was assessed using the DAS-28 PCR tool (Disease Activity Score-28 C-Reactive Protein), classifying as remission a score <2.3, mild activity ≥2.3 to <3.8, moderate activity ≥3.8 to <4.9 and severe activity ≥4.9.

Determination of bone mineral density (BMD)

A G.E. Lunar (Madison, Wisconsin, USA) was used to carry out a scan by dual-energy x-ray absorptiometry in the lumbar spine (L1-4) and in the right and left hips (femoral neck, trochanter and Ward triangle). The latter were added and the average of both hips was determined as a result.

The results of the T-score were interpreted in line with the WHO[8]: T-score ≥-1.0: normal bone mass; T-score between -1.0 and -2.5: low bone mass; T-score <-2.5: osteoporosis. In this study, a T-score of <-2.5 was defined as osteoporosis in the lumbar spine or in the total femur measurement.

Statistical analysis

A statistical analysis was carried out using the SPSS 22.0 package. A value of p≤0.05 was considered a significant result.

The Kolmogorov-Smirnov test was used to determine the normal distribution of variables. The continuous ones were presented as mean and standard deviation or median and interquartile

range, depending on whether or not they had a normal distribution, and were compared with the Student's t test or the nonparametric Mann-Whitney test, respectively. The categorical variables were presented as frequencies and percentages and were compared with the Chi square test.

Finally, a multivariate logistic regression model was used, using the Stepwise Forward regression method to determine the association of the variables studied and the presence of osteoporosis.

Results

A total of 122 women diagnosed with RA were studied. The average age of the studied population was 56.3±10.4 years, with an average disease evolution time of 7.4±3.5 years. Table 1 shows the characteristics of the study population distributed according to the presence or not of osteoporosis. 29.5% had osteoporosis of the femoral or lumbar head. With regard to comorbidities, 35.2% had diabetes mellitus and 18.8% systemic arterial hypertension. Also 8.2% of the population under study were smokers.

Regarding disease activity, 63.1% of the patients were in remission, 31.9% had mild activity, 3.3% had moderate activity and 1.7% had severe activity.

The BMI that prevailed was indicative of obesity (59.8%), followed by overweight (23.7%) and finally normal weight (16.5%). Mean BMI was 30.6±5.5 kg/m^2.

It was found that 54.1% of the patients used glucocorticoids with a minimum of three months; 78.7% used methotrexate and 18.9% used leflunomide.

The results of the evaluated biochemical parameters reported a mean Hb of 12.6±1.3 g/dL 32.8% of the patients presented anemia, the mean of the CRP-Us was 3.4±9.1 mg/dL and that of serum albumin of 4.05±2.5 g/dL. 69.7% presented RF and 10.7% positive CCP.

The mean T-score in the lumbar spine was -1.8±1.5 and the mean BMD in this location was 0.88±0.19 g/cm^2. Low bone mass predominated (36.9%), followed by osteoporosis (32.8%) while 30.3% presented normal bone mass. The mean femur T-score was -0.6±1.4 and the mean BMD was 0.83±0.23. In this location, the criterion of normal bone mass prevailed (63.9%), followed by low bone mass (23.8%) and osteoporosis (12.3%). The characteristics of the densitometric results and the Hb concentrations are summarized in table 2.

A multivariate logistic regression was performed with the presence of osteoporosis as dependent variables, determining its relation with the activity of the disease by DAS-28 CRP ≥2.3, BMI <30 kg/m^2, age >55 years and Hb <12 g/dL. The results are summarized in table 3.

Discussion

We found that patients with RA and anemia ran a higher risk presenting osteoporosis compared to patients with normal Hb, mainly affecting the femoral bone density.

The frequency of anemia found in our population coincides with that reported in the literature[2].

It was found that women who presented a BMI less than 30 kg/m^2 were more at risk of developing osteoporosis. This has been observed in multiple studies, mainly due to the fact that a higher body weight produces a greater mechanical load on the bone tissue, which results in an increase in bone mass. The effect of adipocytes and adipocytokines, such as leptin, waistband and amylin, has also been observed, which can act directly or indirectly on osteoblastic and osteoblastic activity, resulting in the formation of bone mass[9]. On the other hand, adipose tissue indirectly protects against bone loss by providing a source and reservoir of peripheral conversion of androstenedione, which is the active metabolite of estrogen, whose decrease is associated with greater bone loss due to its regulatory effects on the immune system and on the oxidative stages and direct effects on bone cells[10].

When we compared the patients with or without osteoporosis and the presence of disease activity from slight to severe activity, with a cutoff of DAS-28 PCR ≥2.3 points, we found that women with osteoporosis had higher disease activity. This could be due to the impact brought on by inflammation in bone remodeling. The inflammation of the synovial joint increases cytokine expression, as is the case of tumor necrosis factor, IL-1 and IL-6, as well as the stimulating factor of macrophage colonies and the ligand of the nuclear factor activating receptor Kappa-β (RANK), which increase osteoclastogenesis and bone destruction[11]. Based on the principle that the activation of T cells is fundamental for the etiology of RA and the presence of cytokine-like activity in media with activated T cells observed in previous investigations, Rifas et al.[12] conducted a study to identify the factors secreted by T cells that induce IL-6 by osteoblasts, stimulating osteoclastogenesis and osteoclast production independently of RANK. A cytokine was found which they termed SOFAT (secreted osteoclastogenic factor of activating T cells), which may exacerbate inflammation and bone turnover in inflammatory conditions, as is the case of RA.

However, although we found differences between the activity of the disease and the presence of osteoporosis, no significance was found when performing the logistic regression. This may be due to the fact that more than half of the patients were in remission and that most of the patients with activity were of the mild type, with less than 2% being of severe activity.

We found an association between anemia and the development of OF, as reported in the inCHIANTI study[13], which aimed to evaluate the relationship between bone mass and density measurements with anemia, finding that anemia and low Hb levels they are negatively and independently associated with bone mass and density, bordering on trabecular bone density (lumbar T-score) and mainly on cortical bone (T-score femoral).

Table 1. Relationship between the general characteristics and the presence of osteoporosis in women with RA

Variable	Without osteoporosis (N=86)	With osteoporosis (N=36)	p
Age, median (RIQ)	54 (49.3-58)	60 (59-64.7)	0.000*
Mellitus diabetes, %	37.2	30.6	0.48
Systemic arterial hypertension, %	17.4	22.2	0.53
BMI, mean ± SD	31.7 ± 5.3	27.9 ± 5.3	0.001*
Smoking, %	6.9	11.1	0.44
PCR-Us, median (RIQ)	0.9 (0.2-2.5)	0.8 (0.4-1.07)	0.75
Hypoalbuminemia, %	81.4	75	0.42
Time of evolution, median (RIQ)	7 (6-8.75)	7 (5-9)	0.66
DAS-28 PCR ≥2,3, %	26.7	50	0.038*
Use of glucocorticoid, %	50	63.9	0.16
Use of methotrexate, %	80.2	75	0.51
Use of leflonomide, %	17.5	22.2	0.53
APCC, %	10.4	11.1	0.91
Positive rheumatoid factor, %	69.7	69.4	0.97
Anemia, mean ± SD	12.9 ± 1.1	11.8 ± 1.5	0.000*

RIQ: interquartile range; BMI: body mass index; SD: standard deviation; PCR-Us: ultrasensitive C-reactive protein; DAS-28 PCR: Disease Activity Score; APCC: anti-citrullinated cyclic peptide antibodies.
*Significant result.

Table 2. Relationship between serum hemoglobin concentrations and values of lumbar and femur bone densitometry

	Hb <12 g/dL (N=40)	Hb ≥12 g/dL (N=82)	p
BMD lumbar			
Normal bone mass	25%	32.5%	0.44
Low bone mass	40%	37.3%	0.81
Osteoporosis	35%	30.2%	0.61
BMD femur			
Normal bone mass	45%	71.9%	0.003*
Low bone mass	30%	24.4%	0.50
Osteoporosis	25%	3.7%	<0.000*

Hb: hemoglobin; BMD: bone mineral bone density.
*Significant result.

Table 3. Multivariate analysis between risk factors and the presence of osteoporosis in women with RA

	OR	CI al 95%	P
DAS 28 PCR ≥2,3	1.8	0.3-2.1	0.65
BMI <30 kg/m^2	4.1	1.4-11.4	0.009*
Age >55 years	2.2	1.8-5.6-3.8	0.09
Hb <12 g/dL	8.9	3.7-22.4	0.001*

OR: odds ratio; CI: confidence interval; DAS-28 PCR: Disease Activity Score; BMI: body mass index; Hb: hemoglobin.
*Significant result.

Díaz et al.[14] carried out a study on Wistar rats, finding that iron deficiency anemia had a significant impact at the bone level, affecting its mineralization, decreasing the formation of the matrix and increasing its resorption, this associated to the metabolism of the Collagen It has been observed that iron participates in the enzymatic processes involved in the synthesis of collagen, which is an important component of bone tissue since about 90% is composed of collagen type I[15]. It has also been observed that iron is necessary for the metabolism of vitamin D, since the cytochromes that are related to vitamin D use iron to carry out their actions[16].

Another explanation of the relationship between anemia and osteoporosis in patients with RA could be that observed in patients with sickle cell anemia, where bone loss is attributed to hyperplasia, to inflammation secondary to chronic anemia, to hypoxia and ischemia of the bone marrow[17].

Similarly, patients with anemia, regardless of etiology, have a higher degree of hypoxia, which is an important stimulator of bone resorption inducing osteoclastogenesis and later osteoblastogenesis[18].

A study by Rutten et al.[19] in patients with COPD found an association between low Hb levels and the development of osteoporosis, associating it with hypoxia and inflammation.

Among the limitations of our study is the failure to classify morphologically anemia, which could help determine the etiology. Microcytic anemia, for example, could be attributed to atrophic gastritis, which decreases acid secretion and leads to poor absorption of calcium ion, which may contribute to the development of osteoporosis. Furthermore, since this is a cross-sectional study, it cannot ascertain whether osteoporosis occurred before the development of anemia. Another limitation is the lack of determinations of vitamin D and parathormone levels. Finally, the failure to collect the prevalence of fragility fractures, which is the main clinical complication of osteoporosis is a further limitation.

Conclusions

From this study, we may conclude that there is a link between anemia and low bone mineral density in patients with RA mainly in the femoral region, although we cannot infer a causal relationship. Chronic anemia can predispose to bone loss, the development of osteoporosis and increase the risk of fractures. It is important to determine the hematological and bone parameters in our patients with RA, in order to correct Hb values and reduce the risk of fracture.

Conflict of interests: The authors declare they have no conflicts of interest in this study and they have followed all the ethical rules for conducting clinical studies.

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Effect of biological therapy on concentrations of DKK1 and sclerostin, cardiovascular risk and bone metabolism in patients with rheumatoid arthritis

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Summary

Introduction: Previous studies have linked the Wnt pathway in the alteration of bone metabolism and cardiovascular pathology. Also, the control of inflammation with biological therapy has a positive effect on bone mineral density (BMD) and cardiovascular risk. The aim of the study was to evaluate the effect of biological therapy in patients with rheumatoid arthritis, naïve to these therapy, on the inflammatory load and its relation with cardiovascular risk and bone metabolism.

Patients and methods: Prospective cohort study performed in patients diagnosed with active rheumatoid arthritis (RA) initiating biological therapy. Patients were selected consecutively not selected. The serum concentrations of Dickkopf-1 protein (DKK1) and sclerostin were collected, both by means of the ELISA method (Biomedica Medizinprodukte GmbH and Co. KG, Vienna, Austria); demographic and clinical variables, markers of bone remodeling, hip and lumbar spine BMDs were measured by dual energy X-ray absorptiometry (DXA), measurement of intima-media thickness (IMT), evaluation cardiovascular risk by Systematic Coronary Risk Evaluation (SCORE).

Results: 46.7% of patients presented EULAR response to treatment at 12 months. Only in this subgroup of patients, we found in the subgroup of patients an increase in the concentrations of DKK1 following the initiation of biological therapy (baseline 20.55±8.13 pg/ml vs 12 months 31.20±4.88 pg/ml, p=0.03). Regarding markers of bone remodeling, an increase in osteocalcin levels (baseline: 11.25±3.28 ng/ml vs 12 months 15.78±4.11 ng/ml, p=0.01). There was no change in IMT or SCORE at 12 months of treatment.

Conclusions: In patients with RA treated with biological therapy who presented EULAR response we observed a significant increase in serum concentrations of DKK1 at 12 months of treatment not associated with changes in bone metabolism and cardiovascular risk.

Key words: *rheumatoid arthritis, DKK1, sclerostin, biological therapy.*

Introduction

Rheumatoid arthritis (RA) and other inflammatory rheumatic diseases have a higher cardiovascular mortality due to the development of accelerated atherosclerosis[1]. Persistent chronic inflammation, as well as genetic factors, have been implicated in the development of accelerated atherosclerosis and, consequently, in cardiovascular events[2]. Likewise, an increased risk of osteopenia and osteoporosis has been demonstrated in these patients[3,4].

The Wnt pathway has been involved not only in bone metabolism alteration[5], but also in cardiovascular disease[6,7], so it could be one of the common links between these diseases.

Previous studies have found higher serum levels of Dickkopf-1 protein (DKK1) in patients with RA than in the control group, which has been correlated with erosions and inflammation[8]. DKK1 has also been implicated in bone loss brought on by inflammation[9] and vascular calcification processes, with data showing a relationship between DKK1 levels and atherosclerosis in humans[10,11].

Rheumatoid arthritis involvement in this pathway has been explained through the proinflammatory cytokines involved in its pathogenesis, such as tumor necrosis factor alpha (TNFα), or interleukins 1 and 6, which have a significant role in the osteoclastic differentiation process, increasing the receptor activator of nuclear factor kB ligand (RANKL) as well as DKK1 and sclerostin, both Wnt pathway inhibitors[12,13]. Therefore, the control of activity in patients with RA should induce an increase in bone mineral density (BMD), while reducing cardiovascular risk.

Our study attempted to assess the effect of biological therapy in patients with RA who had not previously received biological therapy, on the inflammatory load was analyzed along with its relationship with cardiovascular risk and bone metabolism. To this end, the inflammatory activity, serum concentrations of Wnt pathway antagonists (DKK1 and sclerostin), the presence of cardiovascular risk determined by the modified SCORE method for RA, carotid intima-media thickness and bone disease in patients with RA, at the beginning of treatment with biological therapy and at 6 and 12 months of treatment.

Patients and methods

A prospective cohort study was carried out on patients diagnosed with active RA evaluated in the Rheumatology Unit who initiated biological therapy. The patients were selected consecutively and not selected. To diagnose RA, the 1987 American College of Rheumatology criteria (ACR) were applied. The inclusion criteria were the following: diagnosis of RA; older than 18 years; presence of disease activity defined by the Disease Activity Score 28 (DAS-28) with ESR >2.4 despite treatment with synthetic disease modifying drugs (DMARDs). Signed informed consent was also required. Patients with previous cardiovascular events, previous osteoporotic fractures, metabolic bone disease other than osteoporosis, chronic kidney disease, chronic liver disease, diabetes mellitus type 1 and 2, neoplastic disease, pregnancy and lactation were excluded.

The study was presented and accepted by the Rafael Méndez University Hospital Ethics Committee for Clinical Research. All participants were informed of the type of study and its procedures, and provided their informed consent before any study procedure was carried out. The study was designed and conducted in accordance with the ethical standards of the Helsinki Declaration.

The following variables were collected: serum levels of DKK1 and sclerostin; sociodemographic characteristics; blood pressure (TA); DAS-28 with VSG; Visual analog scale (VAS) of the disease by the patient measured from 0 to 10; duration of the disease determined in months; response of the disease to treatment assessed by EULAR response; rheumatoid factor values and anti-citrullinated peptide antibodies; hemogram; general biochemistry with hepatorenal function; lipid profile (total cholesterol, HDL, LDL, triglycerides); C reactive protein (CRP); calcium and serum phosphorus; parathormone (PTH); 25-hydroxyvitamin D3 (25-OH vitamin D3); markers of bone remodeling (bone alkaline phosphatase, osteocalcin, C-terminal telopeptide of collagen type I -CTX-); thickness of the carotid intima-media (CIMT); SCORE model (Systematic Coronary Risk Evaluation); modified SCORE model for RA; and BMD in the lumbar and hip spine measured by dual X-ray absorptiometry (DXA).

Biochemical determinations

Biochemical parameters were analyzed using standardized techniques.

Calciotropic hormone concentrations were determined by HPLC for 25-OH vitamin D3 and ELECSYS for intact PTH. The biochemical markers of remodeling were determined automatically (Roche Elecsys 2010).

The concentrations of DKK1 were evaluated by ELISA (Biomedica Medizinprodukte GmbH & Co. KG, Vienna, Austria) according to the manufacturer's instructions. The determinations of DKK1 were expressed in pg/ml. Sclerostin concentrations were assessed by ELISA (Biomedica, Vienna, Austria) following the manufacturer's instructions. Sclerostin determinations were expressed in pmol/l, and the lower limit of detection was 10 pmol/l.

Evaluation of disease activity

Disease activity was assessed according to DAS-28 with VSG.

Changes in disease activity were expressed by relative changes of DAS-28 with ESR at 6 and 12 months with respect to baseline, and by the EULAR response to treatment at 12 months.

Bone mineral density assessment

Lumbar spine and femoral neck BMD was evaluated through dual X-ray densitometry (DXA) (Norland XR-800). BMD was defined as the bone mineral content divided by explored area expres-

sed in g/cm^2. For postmenopausal and male patients >50 years, the T-score was used to classify central DXA into normal, osteopenia and osteoporosis. In the rest of the cases, the Z-score was used, considering low bone mass a Z-score <-2.

Changes in BMD were expressed as changes relative per year compared to the baseline.

C-IMT evaluation

Ultrasonographic evaluation of the carotid arteries was carrying out through echo-Doppler (Philips iU22) with a 9-3 MHz linear probe. C-IMT and the existence of plaques were assessed. C-IMT was measured in the distal third of both primitive carotid arteries, 1 cm before the bulb. The plaque was defined as a focal thickening greater than 0.5 mm within the arterial lumen or a thickening >50% of the thickness of the adjacent intima or an intimal thickness >1.5 mm.

BMI changes and the existence of plaques were expressed as relative changes at 6 and 12 months regarding the baseline.

Cardiovascular risk assessment

The patients' cardiovascular risk was determined using the modified SCORE and SCORE model for RA[14]. Those patients who presented plaques and/or c-IMT >0.9 mm in the carotid ultrasound were classified as very high cardiovascular risk patients regardless of the SCORE obtained.

Statistical analysis

The data of quantitative variables are expressed as mean ± standard deviation (normal distribution) or median (non-normal distribution). Qualitative variables data are presented as percentages. The changes in the quantitative variables before and after the treatment were compared with the Student t test for paired samples. The categorical variables were compared through the χ^2 test.

The correlation analyzes between quantitative variables have been carried out using the Pearson (normal distribution) or Spearman correlation (non-normal distribution). The analysis of the association between dichotomous quantitative and qualitative variables was carried out using the Student t test for independent samples (normal distribution) and the Mann-Whitney U test (non-normal distribution). ANOVA was used for polychromatic variables (normal distribution) and K independent samples (non-normal distribution). Values of $p<0.05$ were considered significant. The SPSS program, version 18.0 (SPSS, Chicago, Illinois, USA) was used for the statistical analysis.

Results

Twenty patients who had not previously received biological therapy were included in the study, of whom 18 completed the study at 6 months and 15 patients at 12 months.

Demographic-clinical variables

The average age of the patients was 45.22±14.47 years, with 72.2% being women. 11.1% of the patients included were hypertensive and 44.4% were smokers. The values of the rest of the variables are shown in table 1.

Variables related to the disease

The average duration of the disease was 79.16±69.75 months, median 55.50. The mean baseline DAS-28-VSG was 4.51±1; the number of swollen joints average of 3.33±1.97; the number of painful joints average of 4.39±3.25, median of 5; and the value in the visual analog scale (VAS) of the disease determined by the patient was of 6.52±1.94.

72.2% had positive rheumatoid factor and 83.3% had anti-citrullinated peptide antibodies. 72.2% of the patients initiated biological therapy with anti-TNFα drugs, 22.2% with abatacept and only 5.6% with tocilizumab. 66.7% of the patients included in the study took disease modifying drugs (DMARDs) associated with biological therapy. The average dose of prednisone was 4.86±4.65 mg, median of 5.

Of the 18 patients who completed the 6 months of the study, 44% had an EULAR response at 6 months, and of the 15 patients who completed the study, 7 (46.7%) presented an EULAR response at 12 months.

Analytical variables and related to bone metabolism

The serum levels of DKK1 were of 35.96±36.25 pg/ml, and those of sclerostin 56.09±36.46 ng/ml. Only 6.3% of patients had osteoporosis according to DXA. The values of the rest of the variables are shown in table 2.

Variables related to cardiovascular risk

The right middle c-IMT was 0.55±0.15 mm and the left one was 0.62±0.20 mm. 33.3% of the patients presented carotid plaques. 61.1% of patients had a low SCORE; none presented a high or very high SCORE. However, when applying the modified SCORE for RA, 11.1% of the patients presented a high SCORE, and when performing the carotid ultrasound, 38.9% of the patients were classified with a very high SCORE and 5.6% high.

After 12 months of treatment, no statistically significant changes were found in these variables.

Correlation between bone remodeling, BMD, DKK1, disease activity and c-IMT

No statistically significant correlation was observed between the disease activity measured by DAS-28-VSG and the levels of bone alkaline phosphatase, osteocalcin, CTX, 25-OH vitamin D3, DKK1, sclerostin, BMD (g/cm^2) or the thickness of the intima media. However, we found a correlation between the thickness of the intima media and levels of bone alkaline phosphatase ($p=0.01$, $r=0.6$) and sclerostin ($p=0.05$, $r=0.5$).

Disease activity, measured by DAS-28-ESR, and cardiovascular risk, assessed by means of SCORE, modified SCORE and SCORE by carotid ultrasound, were not related.

Changes in DKK1, sclerostin and markers of bone remodeling after treatment

In the subgroup of patients who presented an EULAR response at 12 months of treatment, we found an increase in DKK1 levels at 12 months of treatment with biological therapy (baseline: 20.55±8.13 pg/ml vs 12 months: 31.20±4.88 pg/ml, p=0.03) (Figure 1), there were no changes in the levels of sclerostin (Figure 2). Regarding markers of bone remodeling, only an increase in osteocalcin levels was detected (baseline: 11.25±3.28 ng/ml vs 12 months 15.78±4.11 ng/ml, p=0.01).

In the subgroup of patients who did not present EULAR response at 12 months of treatment, no changes were found in the levels of DKK1, sclerostin, or markers of bone remodeling.

Changes in bone metabolism and cardiovascular risk after treatment

No statistically significant changes were detected after 12 months of treatment in the BMD (g/cm^2), in the thickness of the intima media (mm) or in the presence of carotid plaques.

Discussion

Our study found a statistically significant increase in DKK1 levels not associated with BMD changes or cardiovascular risk in the subgroup of patients who presented EULAR response at 12 months of treatment.

Different epidemiological studies have shown an association between the loss of bone mineral density, vascular calcification and cardiovascular morbidity and mortality[15-17]. The Wnt pathway is involved in the regulation of vascular calcification and in the differentiation of smooth muscle cells to osteoblasts[18]. Thus, an increase in the expression of DKK1 in carotid atherosclerotic plaques has been resported[19,20], as well as an increase in serum concentrations of sclerostin in patients with atherosclerotic disease and type 2 diabetes[21].

Furthermore, elevated circulating levels of DKK1 have been demonstrated in patients with RA, which were related to radiological damage[8,22-25], and the expression of sclerostin seems to correlate positively with DKK1 levels[9]. However, this is the first prospective study in which the effect of biological therapy on the inflammatory burden of the disease is analyzed, and its relationship with cardiovascular risk and bone metabolism taking into account Wnt pathway inhibitors (DKK1 and sclerostin).

Our preliminary study showed a decrease in DKK1 levels after 6 months of treatment[26], which was in agreement with that published by Briot et al.[13]. In this article, patients with active RA treated with tocilizumab experienced a decrease in DKK1 concentrations, as well as a decrease in markers of bone formation at 3 and 12 months of treatment, not finding changes in the levels of sclerostin. However, our 12-month results showed a statistically significant increase in the levels of DKK1 and ostecalcin in the subgroup of patients who achieved an EULAR response to treatment. These discordant results could be due to the sample size of our study. However, it has recently been reported that anti-TNFα produces in the short term (6 months) an increase in PTH levels and a decrease in DKK1, and that this increase in PTH could promote bone resorption and attenuate the normalization of serum levels of DKK1 in AR[27]. The authors suggest a direct relationship between TNFα and PTH, suppressing TNFα production of PTH. The anti-TNFα, therefore, would prevent this suppression and would lead to an increase in the levels of PTH and, secondarily, of DKK1. In this sense, in our study we found a decrease in serum levels of DKK1 at 6 months, without changes in PTH levels. In contrast, a non-significant PTH increase was detected at 12 months in the subgroup of patients with an EULAR response, which could explain the increase in DKK1 levels. In the case of the study by Briot et al., PTH levels were not analyzed, which could have influenced the levels of DKK1. In addition, most of the patients included in our study initiated treatment with anti-TNFα and only 5% with tocilizumab, so this difference in results could be due to a class effect of the drugs.

It should be noted as limitations of our study, the absence of control group and multivariate analysis, which could have limited the detection of a variable with confusing effect on the results found. However, it should be noted that the demographic, clinical and biological variables were similar both in the group of patients with an EULAR response to treatment at 12 months and in the group that did not present such response.

The follow-up time of patients could have influenced not finding changes in c-IMT and BMD, since published studies have found changes in c-IMT in patients with RA after 2 years of treatment with biological therapy[28]. In the case of BMD, despite studies in which changes were found at one year of treatment, most showed results at 2 years[29].

Table 1. Sociodemographic and clinical characteristics

N	18
Age, mean ± SD	45.22±14.47
Woman, n (%)	13 (72.2)
BMI, mean ± SD	30.39±7.85
HT, n (%)	2 (11.1)
DLP, n (%)	5 (27.8)
Drinking alcohol, n (%)	2 (11.1)
Smoking habit, n (%)	8 (44.4)

SD: standard deviation; BMI: body mass index; HT: arterial hypertension; DLP: dyslipidemia.

Table 2. Biochemical variables related to bone metabolism, disease activity and baseline cardiovascular risk, at 6 and 12 months

	Basal	**6 months**	**12 months**
Total cholesterol (mg/dl), mean ± SD	206±44.36	212.22±54.59 p=0.34	208.13±47.4 p=0.50
HDL-cholesterol (mg/dl), mean ± SD	53.22±11.72	52.40±19.34 p=0.27	51.20±16.4 p=0.72
LDL-cholesterol (mg/dl), mean ± SD	150.44±42.21	155.40±49.40 p=0.44	156±23.88 p=0.54
Triglycerides (mg/dl), mean ± SD	123.72±45.63	138.27±58.62 p=0.23	136.21±37.79 p=0.54
CRP (mg/l), mean ± SD Median	9.98±10.97 5	7.30±8.11 p=0.12 5	8.60±7.68 p=0.57 6
PTH-i (pg/ml), mean ± SD	41.58±17.23	45.23±12.12 p=0.86	49.36±15.89 p=0.12
25-OH vitamin D3 (ng/dl), mean ± SD	19.11±7.94	22.91±15.63 p=0.18	20.68±8.31 p=0.74
Bone alkaline phosphatase (µg/dl), mean ± SD	12.25±4.89	12.22±2.71 p=0.81	12.40±3.83 p=0.78
Osteocalcin (ng/ml), mean ± SD	12.83±5.51	15.59±8.99 p=0.18	17.72±6.52 p=0.002
CTX (ng/ml), mean ± SDE	0.27±0,11	0.32±0.16 p=0.19	1.83±5.80
DKK1 (pg/ml), mean ± SD Median	35.96±36.25 26.56	28.79±17.32 p=0.53 24.71	36.27±20.43 p=0.07 31.28
Sclerostin (ng/ml), mean ± SD Median	56.09±36.46 45.65	89.97±177.68 p=0.31 43.61	59.60±62.47 p=0.4 42.03
BMD (g/cm^2) - L2-L4, mean ± SD - Femoral neck, mean ± SD	 1.19±0.17 0.99±0.13		 1.19±0.22 p=0.22 0.93±0.15 p=0.5
DXA central - Normal, n (%) - Osteopenia, n (%) - Osteoporosis, n (%)	 14 (87.5) 1 (6.3) 1 (6.3)		 10 (83.3) 1 (8.3) 1 (8.3)

Table 2. (*cont.*)

	Basal	6 months	12 months
DAS-28-VSG, mean ± SD	4.51±0.99	3.39±1.36 p=0.001	3.31±1.24 p=0.001
VAS-disease, mean ± SD	6.52±1.94	3.66±2.74 p=0.001	3.20±3.12 p=0.002
Median	7	4	3
SCORE			
- Low, n (%)	11 (61.1)	11 (61.1)	9 (60)
- Moderate, n (%)	7 (38.9)	6 (33.3)	5 (33.3)
- High, n (%)	0 (0)	1 (5.6)	1 (6.7)
- Very high, n (%)	0 (0)	0 (0)	
SCORE modified			
- Low, n (%)	10 (55.6)	10 (55.6)	9 (60)
- Moderate, n (%)	6 (33.3)	5 (27.8)	3 (20)
- High, n (%)	2 (11.1)	2 (11.1)	3 (20)
- Very high, n (%)	0 (0)	1 (5.6)	
SCORE-ultrasound			
- Low, n (%)	8 (44.4)	9 (50)	7 (46.7)
- Moderate, n (%)	2 (11.1)	1 (5.6)	0 (0)
- High, n (%)	1 (5.6)	1 (5.6)	2 (13.3)
- Very high, n (%)	7 (38.9)	1 (38.9)	6 (40)
c-IMT right (mm), mean ± SD	0.55±0.15	0.55±0.16 p=0.92	0.57±0.17
c-IMT left (mm), mean ± SD	0.62±0.20 p=0.10	0.59±0.18	0.61±0.15
Carotid plates, n (%)	6 (33.3)	5 (27.8)	5 (33.03)

SD: standard deviation; PCR: C-reactive protein; c-IMT: carotid intima-media thickness.

In conclusion, we can say that in patients with active RA treated with biological therapy we have observed a significant increase in serum concentrations of DKK1 and osteocalcin, not finding any association with changes in BMD or cardiovascular risk. Therefore, studies with a larger sample size are needed to confirm these results, and to help define the role of DKK1 and sclerostin in RA and in the response to treatment with biological therapy.

Conflict of interests: The authors declare no conflict of interest.
The authors state they have observed the precepts of the Helsinki declaration on clinical studies.

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Figure 1. Changes in DKK1 concentrations after biological treatment in patients who achieved EULAR response

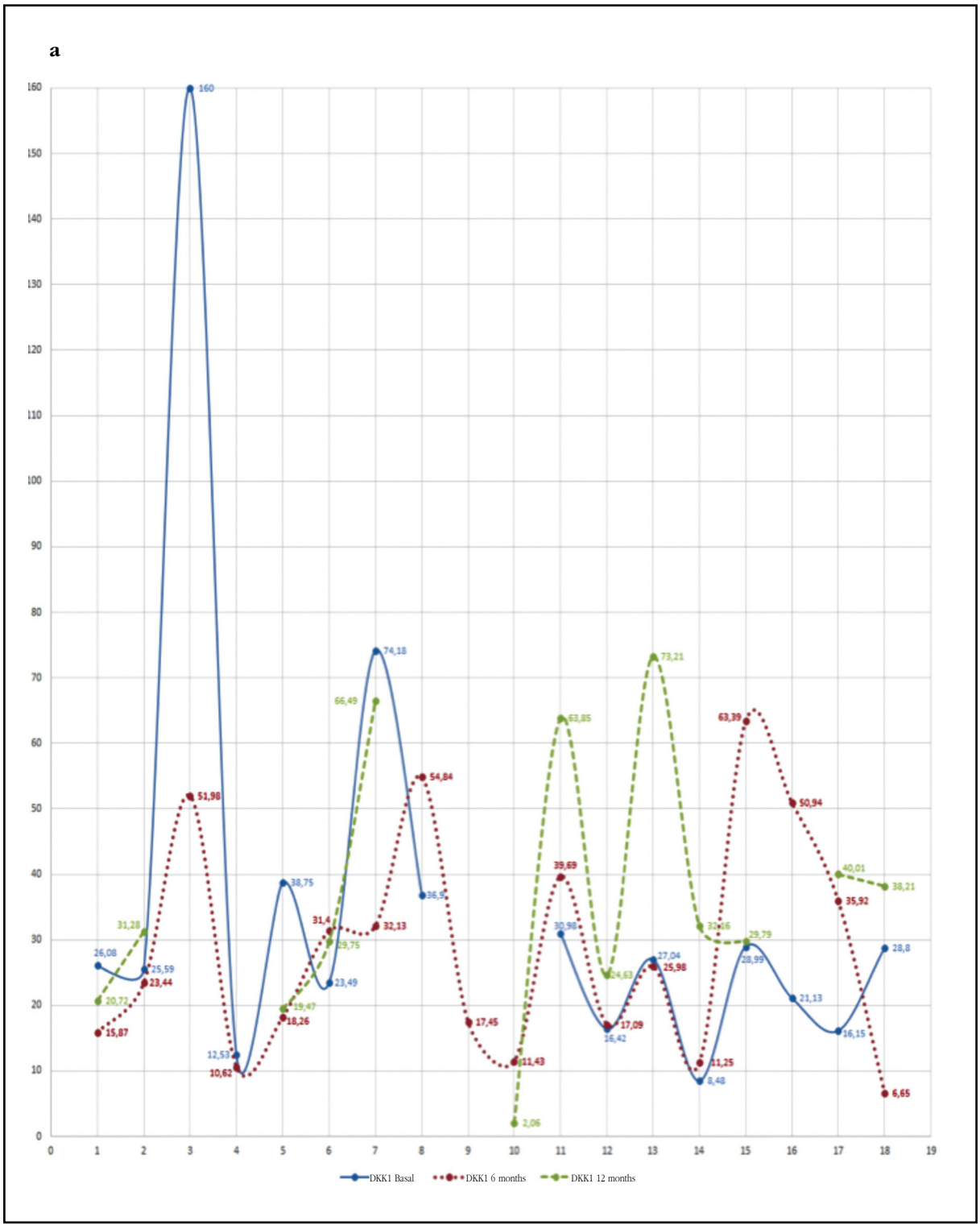

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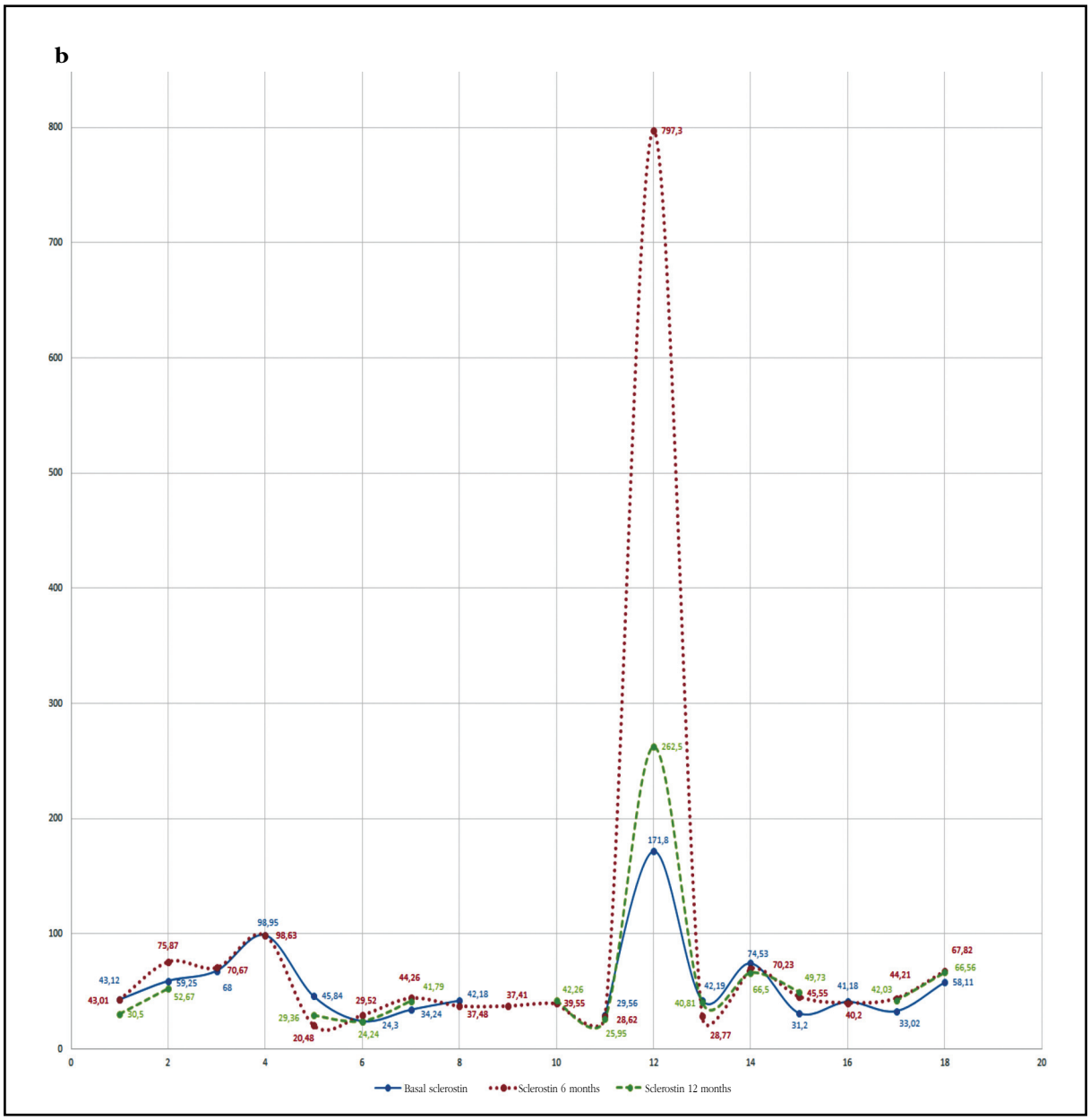
Figure 2. Changes in sclerostin concentrations after biological treatment in patients who achieved EULAR response



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Prevention and early diagnosis of childhood osteoporosis: are we doing the right thing?

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Summary

Objectives: To assess prevention, early diagnosis and training received regarding osteoporosis among the pediatrics professionals in our area.
Material and methods: Survey directed to physicians of pediatricians of Primary Care (PC) and Specialized Care (SC) in order to evaluate their activity in prevention, detection and training received in osteoporosis. The survey was disseminated through the relevant scientific societies.
Results: 420 pediatricians participated (324 from PC and 96 from SC). 93.5% of PC pediatricians and 89.6% of SC pediatricians valued the physical activity of the patients; 85.19% and 35.4% of them, respectively, the intake of dairy products. 45.68% of PC and 70.2% of SC recommended calcium and vitamin D supplements in the case of low nutritional intake, whereas 39.2% of PC and 47.2% of SC favored follow-up. 39.6% of SC pediatricians requested bone densitometry for this disease or risk treatment, and 47.9% measured the levels of 25-OH-vitamin D. 25.93% of PC and 45.3% of SC asked about the existence of fractures, 90.4% and 96.8% requested etiopathogenic mechanism. 40% of PC and 86.2% of SC requested a bone densitometry or referred to the specialist for fractures due to low trauma energy, with specific criteria in 13.7% and 5.86%, respectively. 92% of PC and 82.3% of SC had not received recent training in childhood osteoporosis.
Conclusion: Detection, derivation circuits and the training of pediatricians regarding bone health in our country can be improved. Optimizing these aspects is essential to favor the peak of bone mass in our population.

Key words: *bone health, osteoporosis prevention, early diagnosis of osteoporosis.*

Introduction

Bone mass increases during childhood and adolescence until it reaches its maximum value shortly after puberty[1,2]. Several factors are involved in this process among which the genetic load determines up to 80% while the remaining 20% depends on modifiable external factors, such as nutrition, exercise and exposure to sunlight and osteotoxic substances, among others[3-5]. The optimization of all of them is essential to achieve the maximum bone mass at the end of development[6].

Children suffering from chronic conditions usually have difficulties reaching an optimal peak of bone mass. In general, they present a higher incidence of malnutrition, practice less physical exercise and are less exposed to solar radiation because of their disease[7]. In addition, the inflammatory activity present in some diseases inhibits bone formation and stimulates its reabsorption, as in the case of some medication treatments (especially glucocorticoids)[8].

Several studies indicate that the best way to prevent adult osteoporosis is to favor optimal bone mass peak acquisition at the end of the growth stage[9-11]. Thus, controlling bone mineralization during childhood is an unavoidable obligation for pediatricians, who must promote healthy living habits in their patients, minimize osteotoxic medication use and recognize warning signs to make an early diagnosis if there is bone metabolism disorder.

Our study aimed to evaluate preventive activity and early diagnosis of osteoporosis that is currently carried out, as well as the training received in this field, by primary care (PC) pediatricians and hospital pediatricians who care for children with chronic diseases in our country.

Material and methods

Two online surveys were prepared, one for PC sector pediatricians and the other for pediatricians in specialized care (SC). These surveys collected data on prevention, detection and treatment of children at risk of osteoporosis in routine clinical practice. It also queried them about the training received about this condition.

The surveys were designed using Google Docs technology and disseminated through different scientific societies between November 2014 and October 2015. In addition, in order for the survey to reach the maximum number of physicians, recipients were urged to forward the questionnaire to their pediatric colleagues working in this area. Each participant was sent both surveys indicating that they had to answer one or the other whether they were working in PC or SC activity. A descriptive study of our obtained data was carried out. The results were expressed as percentages. Statistical analysis was carried out using the SPSS v21 package.

Since the surveys did not include patient data and were anonymous and voluntary, ethics committee approval was not required. However, the study was reported to the committee coordinating center, which accepted the approach. The researchers were the only ones who had access to the survey data, which were collected exclusively for statistical purposes.

Results

In all, 420 professionals participated in the survey, 324 PC pediatricians and 96 from different pediatric specialties. The pediatric specialty of those surveyed in the hospital setting is shown in Table 1.

Regarding preventive habits assessment, 93.5% of PC pediatricians and 89.6% of SC reported assessing the patients' amount and type of physical exercise and concerning daily intake of dairy products, 85.2% and 35.4%, respectively. The detailed results are shown in Table 2. Regarding preventive treatment, 45.68% of primary and 70.2% of specialized pediatricians referred to calcium and vitamin D supplements to patients with low nutritional intake of these elements. Complementary test follow-up in the patients who received a supplement was carried out by 39.2% of the PC and 47.2% of the SC.

Regarding the detection of patients with risk of osteoporosis in PC, only 25.93% of professionals asked specifically about fractures within the child health program. 90.43% reported assessing the etiopathogenic mechanism and 40% recognized that SC should be referred to patients with fractures due to low-energy trauma. 94.2% admitted not having specific referral criteria in the presence of osteoporosis (Table 3).

As for managing chronic SC patients, 39.6% reported requesting a dual-energy densitometry (DXA) in case of prolonged corticotherapy or chronic disease that affected the bone although there were no fractures, and 49.7% did not monitor 25-OH-vitamin D levels in patients with risk factors. 86.2% requested DXA or referred to rheumatology or endocrinology for fractures due to commonplace injuries. 13.7% admitted having specific referral criteria in the presence of osteoporosis (Table 4).

In reference to the training received, 92% of PC pediatricians and 82.3% of those of SC had not received training in childhood osteoporosis in the last 5 years, and 88.27% and 79.8%, respectively, considered it insufficient.

Discussion

This is the first reported study of similar characteristics both nationally and throughout European. Our important finding is the great variability of prevention regarding childhood osteoporosis in our environment and the limited training in pediatrics.

The promotion of bone health in the pediatric age is the best strategy for reducing fracture risk and physical disability in old age[12]. The need for osteoporosis prevention programs has been analyzed in different publications on behavior and knowledge in the adult population, although few have been effective[13]. At the school level, programs aimed at improving children's health are carried out, but these interventions are more effective

when they come from the health personnel of reference[13]. Therefore, it is the pediatrician who must identify children and adolescents at risk of presenting or developing low bone mass in order to apply appropriate preventive and therapeutic measures to prevent their progression and the appearance of fragility fractures[13].

The main measures for osteoporosis prevention in childhood are adequate daily intake of calcium and promotion of physical exercise, especially those forms that involve weight bearing[14]. Other beneficial measures include the control of body weight, regular sun exposure and avoiding tobacco and alcohol[14]. Adolescence is the time of greatest bone mass acquisition, so the presence of unhealthy lifestyle habits (low physical activity, decreased intake of dairy products, tobacco, alcohol, etc., relatively frequent at this stage of life) has a very negative impact on its final peak[15]. Therefore, adolescents are the main risk group and the population on which prevention measures should focus, especially on women because of their greater risk of developing osteoporosis in adulthood[13]. So pediatricians should explore patients' living habits and correct those aspects that are harmful to the proper skeletal development in children and adolescents. In our study, most primary care pediatricians reported being interested in their patients' physical activity and dairy intake and reported making specific recommendations to optimize these aspects.

In the case of children with chronic conditions, it is even more important to favor bone mass acquisition by promoting healthy lifestyles. These patients have a special risk of developing osteoporosis in adulthood, since any chronic systemic disorder can influence bone mineral density: nephropathies, metabolic, hematological, endocrinological, gastrointestinal and rheumatological diseases[16-18]. However, in our study, although more than 80% of pediatric hospital specialists were interested in their patients' physical activity, only 34.5% asked about the intake of dairy products as a matter of course.

Table 1. Profile of Specialized Care respondents

Pediatric specialty (n=96)	Percentage of the total (%)
Hemato-oncology	27.1
Traumatology	11.5
Infectology	10.4
Pneumo-allergology	10.4
Neuropediatry	9.4
General Pediatrics	9.4
Digestive and Nutrition	5.2
Nephrology	5.2
Rheumatology	4.2
Cardiology	3.1
Endocrinology	3.1

Table 2. Evaluation of the preventive habits of childhood osteoporosis in the Child Health Program (PC) and in the chronic patient consultation (SC). (n=420 completed surveys)

Question	Percentage (%)			
	PC (n=324)		SC (n=96)	
	Yes	No	YEs	No
Are you interested in the amount and type of exercise that your patients perform?	93.5%	6.5%	89.6%	10.4%
Do you systematically ask how many dairy products your patients consume on a daily basis?	85.2%	14.8%	35.4%	64.6%
Do you recommend the intake of at least 2 glasses of milk per day or equivalent?	94.4%	5.6%	72.9%	27.1%
Do you consider that soy milk, almond, etc., are equivalent to cow's milk as sources of calcium and vitamin D?	9.9%	90.1%	10.5%	89.5%

Table 3. Early detection and referral of PC patients. (n=324 completed surveys)

Question	Percentage (%)	
	Yes	**No**
Within the Child Health Program, do you specifically ask if your patients have had a fracture?	25.9%	74.1%
If a patient reports having had a fracture, do you inquire into the mechanism involved?	90.43%	9.57%
Faced with fractures due to low-energy trauma, does it lead to SC for screening for osteoporosis?	40%	60%
From what number of fractures does your patient refer to Specialized Care for osteoporosis screening?	- 2 fractures: 29.10% - 3 fractures: 51.40% - 4 fractures: 4.19% - 5 or more fractures: 9.26%	
Do you have specific referral criteria for suspected osteoporosis to Specialized Care?	5.86%	94.14%

CHP: Children's Health Program.

Table 4. Management of the chronic risk patient in Specialized Care. (n=96 completed surveys)

Question	Percentage (%)
In the absence of fractures, do you periodically request dual energy densitometry (DXA) or some other imaging test to assess bone mineral density (BMD)?	- yes: 1.1% - if prolonged corticosteroid therapy: 16.7% - if chronic pathology that affects BMD: 7.3% - if prolonged corticotherapy and/or chronic condition affecting BMD: 39.6% - no: 35.4%
In the absence of fractures, do you periodically request levels of plasma 25-hydroxyvitamin D3 in your patients with risk factors?	- yes: 7.3 % - yes, if factors of hypovitaminosis D: 51.1% - no: 41.7%
Do you specifically ask your patients if they have had a fracture since the last visit?	- yes: 45.3% - no: 54.7%
If they have suffered one, are you interested in the mechanism involved?	- yes: 96.8% - no: 3.2%
If it seems a low-energy trauma to cause a fracture, do you request DXA or refer the patient to specialized care for osteoporosis screening?	- yes: 86.2% - no: 13.8%
From what number of fractures does DXA request or refer its patients to specialized care for osteoporosis screening?	- 2 fractures: 72.4% - 3 fractures: 23% - 4 fractures: 2.3% - 5 or more fractures: 2.3%
Do you have specific referral criteria for suspected osteoporosis to specialized consultation?	- yes: 13.7% - no: 86.3%

The appearance of low impact fractures (resulting from bone fragility) means a significant decrease in bone mineral density, and appears in established phases of the disease[1-3]. Therefore, the active search for children at risk is important, including in the medical history of child health programs, the assessment of the fractures they present and the monitoring of calcium and vitamin D levels. In our study, the low percentage stands out of pediatricians of PC that include in the case history the number and characteristics of the fractures of the child referred to SC for low impact fractures. On the other hand, more than half of SC pediatricians do not monitor vitamin D levels or bone mineral density in the chronic risk patient, although most assess the etiopathogenic mechanism and report the reference units of their center.

As for calcium supplements, multiple studies restrict their use to individuals with insufficient contributions through diet, not supporting systematic supplementation neither in healthy children nor with osteoporosis if they have an adequate contribution[19-22]. Similarly, there are no data that allow us to systematically recommend supplementation with vitamin D[23,24]. However, calcium and/or vitamin D supplements are recommended when the contribution of these elements is low at baseline. Adequate levels of vitamin D3 (25-OH Vitamin D) in childhood are between 20 and 30 ng/ml (75-50 nmol/l), although recent studies place optimal levels above 30 ng/ml. ml (75 nmol/l)[27,28]. The recommended daily amount of vitamin D3 and calcium is shown in table 5. In the case of vitamin D, we can measure its plasma levels (25-OH vitamin D), while the calcium intake should be estimated by means of a dietary survey. In our study, only half of the PC pediatricians and 86% of SC referred to calcium and vitamin D supplements in these situations. Such supplementation implies the need to control plasma levels and to detect possible complications, such as hypercalciuria, renal lithiasis or cardiovascular complications[29,30]. In our study, it is noteworthy that most pediatricians of both groups did not carry out analytical monitoring or follow-up with complementary examinations during treatment.

In terms of managing childhood osteoporosis guidelines, the European Society of Children's Endocrinology[28] and International Society of Clinical Densitometry (ISCD)[29] have published recommendations as has the nutrition committee of Spain's Pediatric Society on infant nutrition and bone health[30]. Despite this, most of the respondents from both the PC and SC groups reported that they lacked specific protocols to address this condition and referral networks for these patients, both at outpatient and hospital levels.

Furthermore, the training of our physicians regarding bone health is limited, the percentage being lower in PC pediatricians, a fundamental pillar in child care. In addition, most pediatricians in both areas consider their training on these aspects to be inadequate.

The main limitation of our work is that we could not ascertain the percentage of participation, since the surveys were not only disseminated by different scientific societies, but the participants were encouraged to forward the survey to their pediatric contacts who might be interested in taking part. Even so, taking into account the total pediatricians with healthcare activity in our country, we consider that the number of surveys implemented could be improved.

In addition, participation was voluntary, so it is likely that there is a certain participation bias. The physicians were more aware of the issue in question and responded to the survey. In any case, this does not invalidate the main conclusion of the study: the great variability in the approach of this entity.

In conclusion, the preventive activity in relation to childhood osteoporosis that is carried out in our environment varies greatly, and the training that pediatricians receive concerning osteoporosis is very scarce. In addition, there are no specific protocols in our environment to address children at risk. Consequently, adequate prevention and treatment measures are not being carried out in our child population, especially in patients with chronic disorders.

It is essential to optimize these aspects and involve pediatricians in detecting and preventing children at risk, to promote the maximum peak of bone mass in children, and thus reduce the incidence of osteoporosis in the future.

Conflict of interests: The authors declare no conflict of interest.

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Table 5. Recommended daily amount of calcium and vitamin D3 in the child population

Group	Daily amount
Healthy children	400 IU vitamin D3 Calcium: 700 mg from 1 to 3 years 1,000 mg from 4 to 8 years 1,300 mg from 9 to 18 yearss
Children at risk	400 to 1,000 IU of vitamin D3 Higher doses of calcium
Children with hypovitaminosis D	2,000 IU of vitamin D3 per day for 6 weeks, increasing from 4,000 to 6,000 IU per day for 6 weeks if they associate malabsorption, obesity or treatment with drugs that accelerate the catabolism of vitamin D

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Summary
Prostate cancer is the most common non-cutaneous malignant lesion in males over 70 years of age. Diagnosis in advanced stages of the disease is not exceptional, through metastatic lesions as debut. The most characteristic of these lesions are osseous with osteoblastic behavior, uncommon in maxillary bones. On the other hand, Paget's disease is a chronic metabolic disorder attributed to osteoclast dysfunction. At the craniofacial level, the characteristic affectation is an increase in size, a "cotton flakes" pattern or circumscribed osteoporosis. The fact that this is only located in the mandible is exceptional.
A case of Paget's disease of the right hemi-mandible bone is presented in which a metastasis is developed due to prostatic adenocarcinoma.

Key words: *Paget's bone disease, osteitis deformans, prostate cancer, metastasis, oral neoplasms.*

Introduction

Prostate cancer (PC) is the most common non-cutaneous malignant lesion in men over 70 years. There is genetic predisposition and several exogenous factors have been proposed, but without sufficient evidence to recommend lifestyle changes that might prevent PC. Screening programs are controversial, by digital rectal examination and prostate-specific antigen (PSA) levels, with individualized strategies suggested based on the risk profile. The eco-guided biopsy is standard for diagnosis, corresponding in more than 95% of cases to acinar cell adenocarcinoma[1].

On the other hand, Paget's disease of bone (PDB) is a chronic condition of unknown cause due to osteoclast dysfunction, with increased bone remodeling that triggers bone growth and disfigurement. It presents genetic susceptibility, is more predominant in Caucasians, slightly more frequent in males and exceptional in individuals under 40 years. No cure has been found, although bisphosphonates are usually prescribed depending on metabolic activity and symptomatology[2-5].

Clinical Case Report

A 77-year-old man, ex-smoker of 20 packs per year, ex-drinker of 7 units of standard drink/day until 2 years previous, and with a history of high blood pressure, ischemic stroke and intervening left carotid stenosis. His treatment was standard with atorvastatin, valsartan, hydrochlorothiazide and clopidogrel reported. He was diagnosed with stage IV prostate adenocarcinoma Gleason 3+4, with PSA values of 110.47 ng/mL and alkaline phosphatase (FA) of 142 U/L initially, and bone metastases in vertebrae C7 and D1. The serum levels of calcium, phosphorus and parathyroid hormone were within normal limits and treatment began with complete androgen blockade. After 19 months, he presented right hemifacial swelling, with bulging of both cortical of the ipsilateral mandible branch (Figure 1) and without ulceration of the oral mucosa upon examination. The pathological anatomy provides a new diagnosis of PDB in mixed phase, without data suggestive of malignancy (Figure 2). There is no suspicion of involvement in other skeletal regions.

Figure 1. Orthopantomography. Irregular sclerosis of right hemimandible. Widening of adjacent periodontal spaces

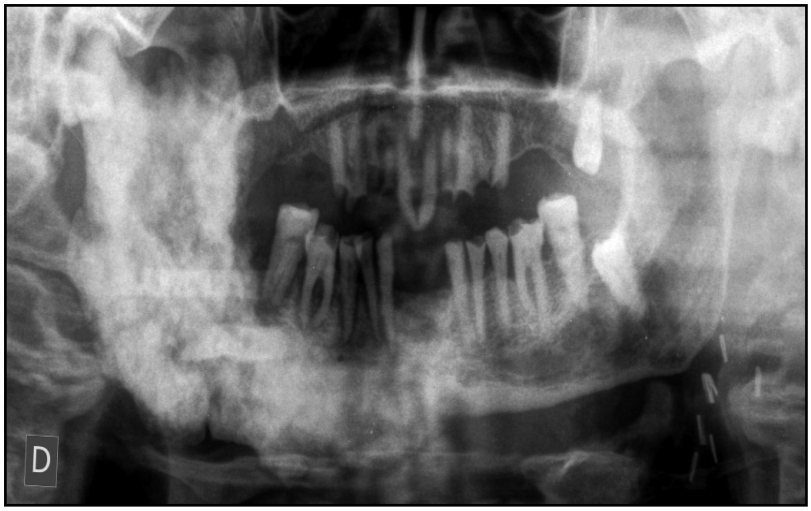
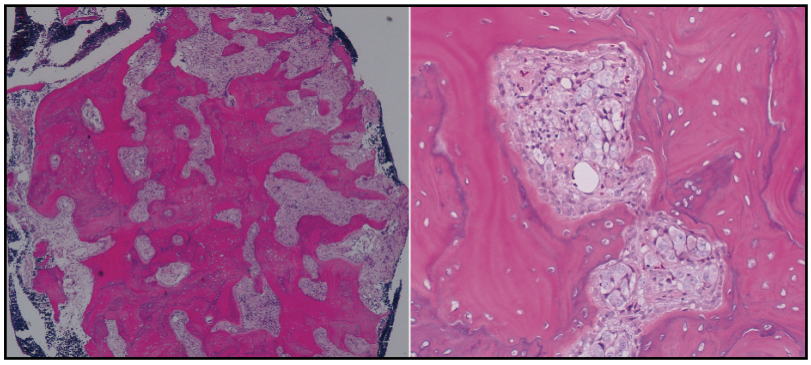


Figure 2. Hematoxylin & Eosin 10x, 200x. Loss of demarcation between cancellous and cortical bone. Hyperostosis with mosaic pattern, increased bony trabeculae and prominent basophilic lines. Multinucleated osteoclasts and isolated eosinophilic intranuclear inclusions. Bone marrow with fibrous stroma

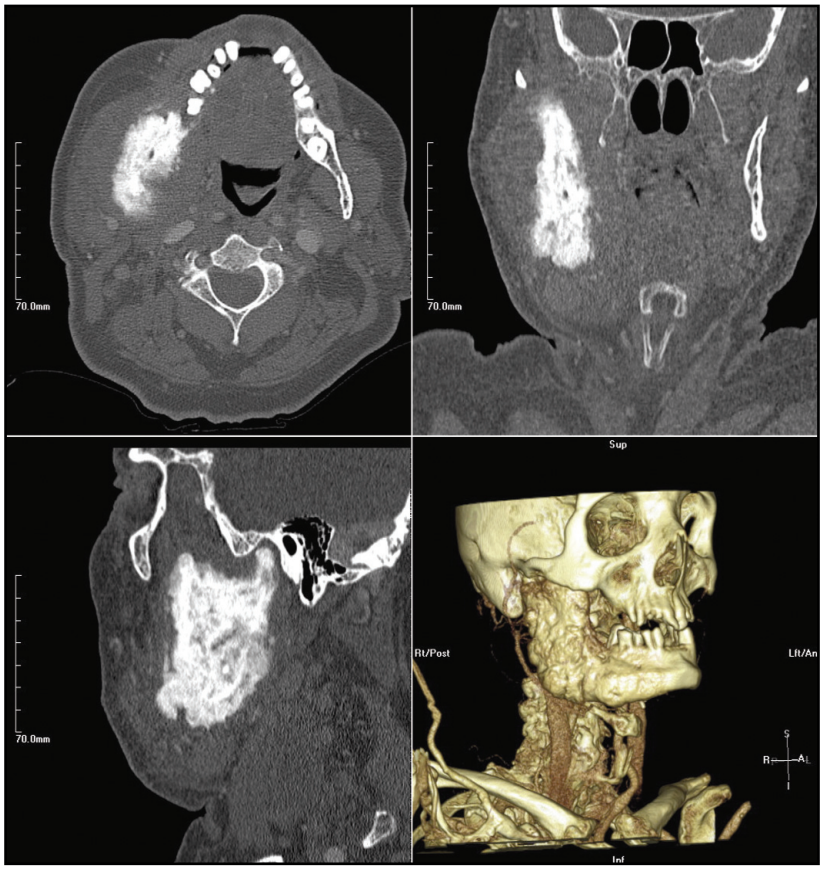


He did not receive treatment for symptomatic stability until 11 months later, when the maxillofacial clinic is accentuated. Radiologically, sclerotic intensification with mandibular bone growth, soft tissue increases in masticatory space, as well as lymphadenopathies in right cervical Ia and Ib levels (Figure 3). A new submucosa biopsy of soft tissues and bone showed fibrous tissue with changes of sclerosis and intense artifact, with infiltration by malignant cells of epithelial aspect positive for CK, AE1/AE3 and PSA. In addition, he is diagnosed with a new bone metastasis at the level of the left iliac blade. Chemotherapy is ruled out, and two doses of 20 Gy of radiotherapy are applied with an antalgic intention in the jaw and pelvis.

After 9 months, in a control bone scan, new metastatic foci are seen in right orbit, ribs on both sides, sacral column, left humerus, both scapulae and right femoral diaphysis. He underwent surgery with intramedullary rod for femoral neck fracture. The patient died 46 months after the initial oncological diagnosis, following prolonged bed rest at home.

Discussion

Figure 3. Computerized tomography. Axial, coronal, sagittal and 3D. Corticomedullary sclerosis with soft tissue enlargement surrounding the right hemimandibular branch.



According to the literature, 3% of intraoral malignant lesions correspond to metastasis. The most frequent regions affected are the mandible in the molar area, with its rich vascular supply and a remnant of bone marrow in adults and the gum adhered to soft tissues. In many cases, these are late complications of advanced malignant disease with multiple visceral metastases, although up to 25% of cases are the first manifestation. Globally, the most common primary cancers in the maxillary bones are those of the breast, while in soft tissues they are those of the lung. In males, maxillary metastases of prostatic origin correspond to 11%, versus 1.5% in soft tissues. Inflammation, pain, sensitive alterations of relatively rapid evolution, or a bleeding exophytic hyperplastic lesion are usually the usual symptoms, which can easily be misinterpreted as benign pathology. The histology may simulate primary intraoral neoplasms, especially those poorly differentiated originating in salivary glands, requiring additional immune-histochemical and molecular techniques[6,7].

In cases of PC, the Gleason scale allows, together with the TNM staging, to establish risk groups. To assess the locoregional extension, magnetic resonance is generally employed, while for remote extension, computed tomography and bone scintigraphy are used, where the most characteristic metastases are located[1]. PC cells frequently secrete factors that promote bone formation, such as bone morphogenic proteins (BMPs), and RANK-L inhibitors, attenuating osteoclastic action[6]. Therefore, most metastases will be osteoblastic although they have also been reported in a mixed, osteolytic form, even without radiological evidence. As with other mandibular neoplasms, diagnosis is not unusual after pain or paresthesia-hypoesthesia of the inferior dental nerve that does not improve after dental treatments[8-11]. They have not only been reported at mandibular level, but also in branches[12], condyles[13] and parotid glands with bone infiltration[14].

The number and location of bone metastases in PC are among the most commonly used but not validated prognostic factors, in addition to visceral metastases, the Gleason score, PSA and AF. The usual management is androgen blockade combined or not with chemotherapy. The prescription of bisphosphonates, radiotherapy, even cytoreductive surgeries or metastasectomies to improve quality of life is recognized for palliative purposes[1].

As for PDB, the location is segmental, monostotic or polyostotic, most common in the pelvis, femur, spine, skull and tibia, although it can affect any bone and may present with pain, arthralgias and compression syndromes. There is an increased risk of fracture and malignancy. It is asymptomatic in many cases, carrying out the diagnosis when complications appear or characteristic radiological images. The Paget-affected bone presents vascular alterations, with regional vasodilatation, which could increase cardiovascular risk. The bone scan allows us to assess the extension. In the active phase of the disease, though not a specific datum, serum FA increases along with other replacement markers. Histology usually shows a mosaic pattern, with areas of osteoclastic and osteoblastic activity. Multinucleated osteoclasts and cytoplasmic or intranuclear inclusions are more typical of the initial rest phase. In addition, it presents with bone marrow fibrosis and arteriovenous shunts[3-5].

Increased cranial size, a "cotton flakes" pattern or circumscribed osteoporosis, are the most characteristic findings at the head level of the PDB, with singular mandibular involvement considered exceptional. The teeth erupt mispositioned and migrate with bone growth, showing in radio-

graphs both radiolucent areas as of hypercementosis or ankylosis of roots. In these cases, the extractions are complex, alveolar healing is slow with localized osteitis, and there is an increased risk of secondary osteomyelitis. Loco-regional surgical remodeling has its role, and additional precautions should be taken to control haemostasis and infections with optional oral surgery[5,15,16].

Bisphosphonates slow the differentiation of common precursor cells, promote apoptosis and suppress bone resorption by osteoclasts, hence their indication in active PDB and in symptomatic bone metastases. They also have anti-angiogenic properties and a half-life of up to 11 years after bone incorporation. Before starting treatment, whatever the disease and route of administration, a dental examination and extraction of periodontal teeth on or adjacent to the lesion, in order to prevent osteonecrosis are recommended[2,17-19].

The main differential diagnoses of craniofacial PDB are fibrous dysplasia and fibro-osteomas[5]. In the present case, as there was a recent change in the lesion with a soft-tissue component, sarcomatoid malignancy would also be included, with osteonecrosis being less likely due to the lack of a history of bisphosphonates, anti-angiogenesis and radiotherapy. However, due to the vascular alterations and the compromised scarring of the Pagetic bone, spontaneous osteonecrosis could be triggered[20]. Although the patient developed unfavorably, it has been shown that PC and PBD association delays metastatic progression and increases overall survival[21].

Conclusions

Metastatic PC is not uncommon in our setting, with a high survival rate. The mandibular location of this oncological or other lineage is a challenge for both clinicians and pathologists. Occasionally, the overlap of bone disease can hinder diagnosis even more, highlighting metabolic disorders, both training and recovery, and the side effects of therapies, such as osteonecrosis.

Conflict of interests: The authors declare no conflicts of interest.

The precepts of the Helsinki declaration on clinical studies have been observed throughout this research work.

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Osteoporosis and spinal surgery: strategies for medical and surgical treatment

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Summary

The prevalence of osteoporosis in patients undergoing spinal surgery is estimated at 50% in women over 50 years, a higher figure than in the general population adjusted for age. Consequently, many authors recommend the systematic assessment and timely treatment of osteoporosis in most patients who are going to undergo arthrodesis.

The decrease in bone mineral density (BMD) is the main factor in independent risk related to the failure of the instrumentation in spinal fusion surgeries.

Complications arising from spinal fusion are more frequent in osteoporotic patients over 65. The most frequent early complications are pullout or tearing pedicular screws, pedicular fracture and fracture by compression in the adjacent vertebral segment. After 3 months, the most frequent complications are pseudoarthrosis, fracture or mobilization of the bars, subsidence of vertebral intersomatic boxes and the kyphosis of the proximal joint.

There are some clinical trials of spinal arthrodesis surgery with perioperative treatment with alendronate, zoledronic acid, or teriparatide that have been shown to be effective in clinical improvement and increase in fusion rates.

Several modifications in the surgical arsenal may improve fusion rates and decrease surgical complications. Arthrodesis has been highlighted with cemented and expandable pedicle screws.

Finally, randomized clinical trials have shown that vertebral reinforcement treatments in osteoporotic vertebral fractures are beneficial in the short and long term.

Key words: *osteoporosis, vertebral arthrodesis, lumbar spine, spinal fusion.*

Bone metabolism and spinal disorder

Spinal fusion surgeries with or without instrumentation have become well-established surgical procedures in the therapeutic arsenal of spinal disease, either degenerative, deformity (scoliosis and degenerative kyphosis), vertebral instability (degenerative spondylolisthesis and isthmus) and in stenosis of the lumbar spinal canal (central or foraminal).

The gradual aging of the population has led to an increase in spinal fusion surgeries in elderly patients. From 2001 to 2007, spinal fusion procedures in those insured by Medicare in the USA increased 15 fold[1]. A significant percentage of patients who require lumbar or cervical vertebral arthrodesis are older than 50 years, many of whom suffer from osteoporosis without being correctly diagnosed.

In Spain, approximately 2 million women suffer from osteoporosis, according to the densitometric criteria proposed by the World Health Organization (WHO). Díaz-Curiel et al. estimated that the prevalence of osteoporosis in Spain is around 26% (1 in 4) of women over 50 years of age[2].

In a recent study in patients over 50 years who underwent spinal surgery, 41.4% of women were reported to have osteopenia and 51.3% had osteoporosis. On the other hand, in men, 46.1% presented osteopenia and 14.5% osteoporosis[3,4]. Thus, the prevalence of osteoporosis in women undergoing spinal surgery is higher than that of the general population adjusted for age. Consequently, many authors recommend the systematic evaluation and timely treatment of osteoporosis, especially in women over 50[3].

Patients with osteoporosis present a lower bone mineral density (BMD) and lower osteoblastic activity, which negatively influence osteoconductive, osteoinductive and osteogenic capacity. Therefore, patients with osteoporosis have increased bone remodeling and negative final bone balance, which results in poor bone fusion, and a reduction in the force of extraction or pullout of the pedicle screws[4].

Reduced BMD is the main independent risk factor related to instrumentation failure in lumbar fusion surgeries4 and a moderate risk factor for the development of pseudoarthrosis. BMD is significantly higher in patients who achieve higher fusion rates compared to those who suffered from a lack of fusion after vertebral column arthrodesis, according to some reports[5]. Although the development of pseudoarthrosis is multifactorial, a significant proportion could be explained by low BMD levels[6].

Complications in spinal surgery associated with osteoporosis

Arthrodesis with long instrumentation assemblies are increasingly common in the treatment of spinal deformity (scoliosis and degenerative kyphosis). Scoliotic deformities are present in 36-48% of osteoporotic women and patients with large deformities in the spine usually have a low BMD[7]. Complications derived from spinal fusion surgery tend to be more frequent in patients over 65 and osteoporotic.

Early complications occur within the first 3 months of surgery. The most frequent are the pullout or removal of the pedicle screws, epidural hematoma, pedicular fracture and fracture of the adjacent vertebral segment by compression mechanism[7-10].

Late complications, after 3 months include pseudoarthrosis, fracture or mobilization of the bars, fracture by compression mechanism of the adjacent vertebral segment, pain in the iliac area (specifically in the area of insertion of the iliac screws), disc herniation (mostly cephalic), subsidence of vertebral intersomatic boxes and proximal junction kyphosis (PJK) (Figure 1).

Instrumentation failure may also be subdivided according to the location of the instrumentation, either anterior or posterior. The latter tends to fail due to a limited fixing force in the bone of low density, which results in the extraction or pullout and/or loosening of the pedicle screws[11,12]. In contrast, anterior instrumentation is subject to a repetitive cyclic load, resulting more frequently in screw rupture or implant subsidence in patients with BMD involvement[12,13].

Osteoporosis is a major risk factor for the failure of surgery in the spine, and even more so when multiple vertebral levels are instrumented[14,15].

De Wald et al.[10] reported that the two most frequent mechanisms of complications in patients over 65 years of age, operated on at least 5 levels of instrumentation, were vertebral fracture by compression mechanism of the last superior vertebral segment of an arthrodesis and PJK to the last instrumented segment in 28% of cases. Other articles concur that PJK is the most frequent complication in multi-level instrumented columns[16-18]. As a complication, PJK has provoked much interest in its frequency and complexity. The Scoliosis Research Society defines proximal junctional kyphosis (PJK) as the kyphotic Cobb angle equal to or greater than 20º between the last instrumented vertebra and the two vertebrae located above (Figure 2). PJK occurs in 39% of operated deformities occurring most between 6-8 postoperative weeks. The three most important risk factors are advanced age, poor bone quality and significant sagittal imbalance prior to surgery. Of all the patients who develop PJK, approximately one third are re-operated early before 5 months for surgical revision due to mechanical failure and vertebral instability[19].

It is important to consider that a preoperative thoracic kyphosis of more than 30º is an independent risk factor for the appearance of PJK, and that the adequate resolution of the sagittal imbalance prior to surgery reduces the incidence of PJK from 45% to 19%[20].

Medical treatment strategies

Patients with osteoporosis and with uncorrected hypovitaminosis D reported present worse rates of

bone fusion after vertebral arthrodesis and may also have poorer clinical results in disability scales in the perioperative period[4].

In recent decades there has been a significant advance in the knowledge of the pathophysiology of bone formation and resorption, as well as in the treatment of osteoporosis, which logically leads us to wonder about the influence of these therapies in the bone fusion process in spinal surgery[21]. Currently an increasing number of studies and clinical trials evaluate the impact of various pharmacological treatments (bisphosphonates, zolendronic acid, PTH) on bone fusion in spinal surgeries. Table 1 summarizes the main studies to date.

In experimental animals, 18 studies have been reported that assessed the influence of bisphosphonates on the fusion process in arthrodesis, most of them did not demonstrate significant effects on bone fusion rate probably attributed to low statistical power. Studies in animals with bisphosphonate-based therapy showed that the bone fusion mass was histologically less mature, however the impact on spinal biomechanics was not clear[22].

On the other hand, in an osteoporotic animal model alendronic acid was found to be effective in obtaining radiological, biomechanical and histological improvement of the fusion of the vertebral column[23]. Alendronate increased the biomechanical strength with internal bone growth in the posterolateral fusion masses in the osteoporotic animals. This study suggests that alendronate can help achieve successful fusion of the spine in animals affected by osteoporosis.

Kim et al.[24] studied the effect of alendronate in 44 patients operated on 1-level instrumented intersomatic lumbar fusion compared to the control group without treatment. They did not find significant differences in terms of bone fusion, and instead there was a higher incidence of vertebral plate degeneration in the alendronate group.

Nagahama[25] published a clinical trial in 40 patients with osteoporosis who underwent intersomatic lumbar fusion and treatment with bisphosphonates. There was an increase in the fusion rate at one year of follow-up in the alendronate group compared to controls (95% vs 65%, respectively), in addition to reducing the presence of subsidence of the prosthesis and the vertebral fracture of the level adjacent. Finally, the authors recommend postoperative treatment with bisphosphonates in all patients with osteoporosis, although they acknowledge that there is still no consensus regarding the use of these drugs.

Figure 1. (A) Lateral radiograph of lumbosacral spine: S1 screw rupture is observed (arrow). (B) Surgical part of the broken screw removed. (C) side of the lumbosacral spine where mobilization bar distally (arrow) x. (D) CT axial cut and (E) sagittal, hypodense halo is observed around the pedicle screws (arrows), characteristic of pseudoarthrosis. (F) Sagittal CT that illustrates the presence of subsidence or subsidence of the intersomatic device, note the loss of the disc height and the erosion of the vertebral plates (arrow)

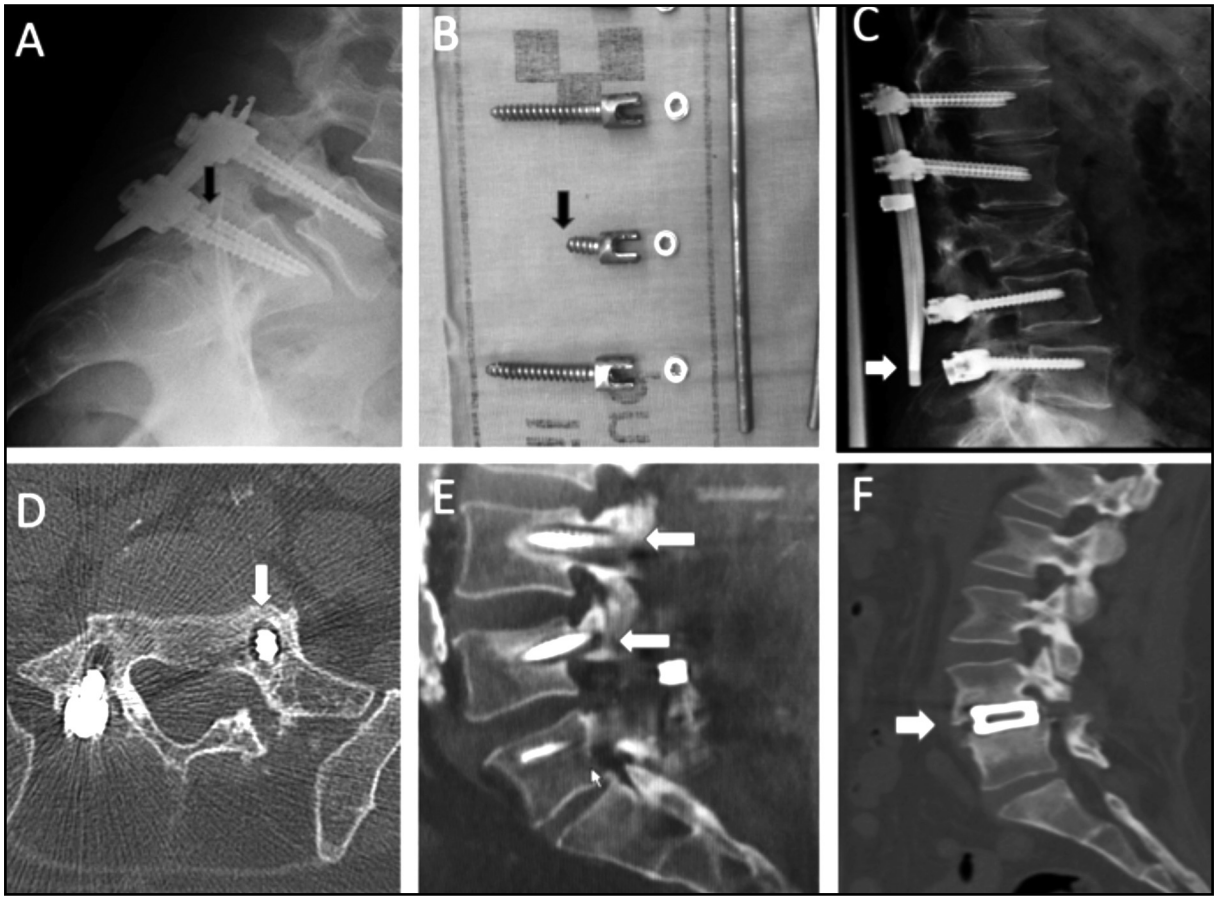
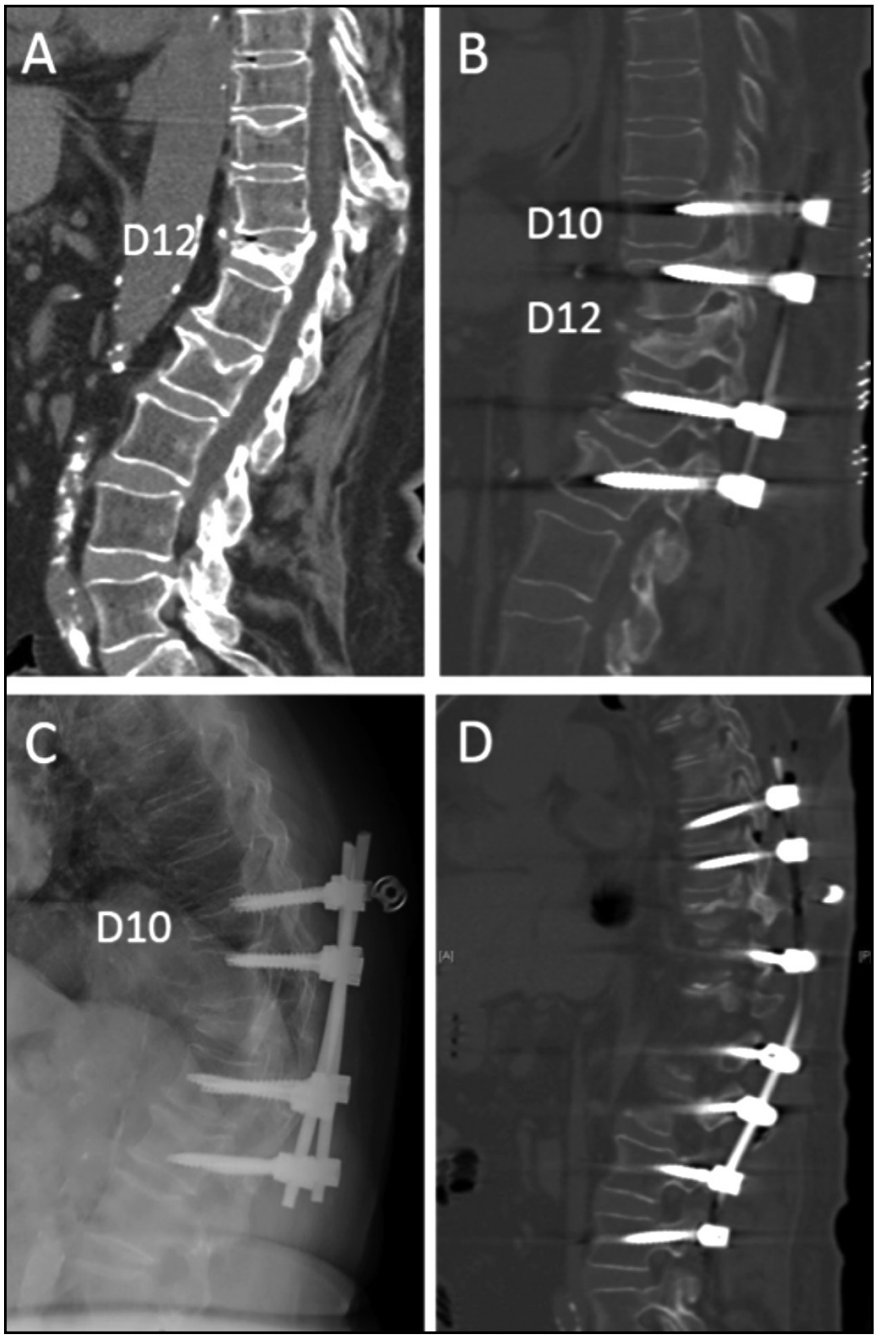


Figure 2. (A) Sagittal CT at the thoracolumbar level; osteoporotic compression fracture at level D12 with segmental kyphosis is observed. (B) Arthrodesis through instrumentation with pedicle screws from D10 to L2, with significant kyphosis correction. (C) Lateral radiography: vertebral compression fracture at D10 level with kyphosis of the proximal junction and screw pullout at level D10. (D) Extension of arthrodesis, superior to levels D8 and D9 and inferior to levels L3 and L4, and correction of kyphosis



Park et al.[26] in 2013 evaluated the effect of zoledronic acid in 44 patients with lumbar spinal stenosis operated on posterolateral arthrodesis with instrumentation of 1 or 2 levels, one group received a dose of zoledronic acid and another group control. At 6 months after surgery there was no significant increase in the fusion mass in the single-dose zoledronic acid group demonstrated by 3D computerized tomography. However, there was a significant improvement in the Visual Analogue Scale (VAS) and the Oswestry Functional Scale (OFS) in the zoledronic acid group.

Tu et al.[27] also studied the effect of zoledronic acid on fusion rates in patients with osteoporosis after posterior lumbar interbody fusion at 2 years of follow-up. The zoledronic acid group received an intravenous infusion at 3 and 12 months after surgery. There was a non-statistically significant difference in patients with zoledronic acid with a fusion rate of 75%, compared with 56% in the control group. In addition, there were better VAS and OFS scores, but without being statistically significant in patients receiving zoledronic acid. The rates of pedicle screw loosening were significantly lower in patients with zoledronic acid of 18% compared to 45% in the control group.

Chen et al.[28] conducted a recent randomized clinical trial on the effect of zoledronic acid on bone fusion in patients with osteoporosis after arthrodesis of the lumbar spine. They studied 79 patients with degenerative spondylolisthesis of 1 level. A greater fusion was observed at 3, 6 and 9 months in the zoledronic acid group without being significant at 12 months. Zoledronic acid prevented bone loss induced by immobilization and increased BMD. The authors concluded that zoledronic acid shortens the time to achieve a bone fusion, and prevents subsequent vertebral compression fracture. The limitations were the small sample size and the short follow-up time.

Another randomized clinical trial was conducted by Ohtori et al.[29] in 57 women with osteoporosis and degenerative spondylolisthesis undergoing a posterolateral arthrodesis procedure. One group received risedronate and another parathyroid hormone (teriparatide). The authors found a fusion rate of 82% with PTH and 68% with risedronate; the time frame for carrying out bone fusion was 8 months for PTH and 10 months with risedronate.

Table 1. The prevention and timely treatment of osteoporosis is the most important principle

Study	Population	Medical treatment (groups)	Duration of treatment	Fusion rates	Fusion valuation method
Alendronate Kim et al.[24]	44 patients with OP who operated from PLIF	- Alendronate sodium (35 mg/week) - Control group	Not specified	- Alendronate: 66.7 - Control group: 7.9%	X-ray: fusion with bone bridges between vertebral bodies, inside or around the intersomatic boxes and angular movement less than 5° in dynamic X-ray
Alendronate Nagahama et al.[25]	40 patients with OP with 1-level PLIF intersomatic fusion	- Alendronate sodium (35 mg/week) - Alfacalcidol (1 mg/day)	1 year	- Alendronate: 95% - Alfacalcidol: 65% (p=0.025)	Coronal and sagittal CT to evaluate bone bridges
Zoledronate Park et al.[26]	44 patients with stenosis Symptomatic lumbar spinal undergoing lumbar fusion Posterolateral of 1 or 2 levels	- 1: Autologous posterolateral fusion iliac crest and zoledronic acid (5 mg) - 2: Local allograft and autograft and Zoledronic acid (5 mg) - 3: Autograft with iliac crest and local bone only - 4: Local allograft and autograft	2 weeks after surgery a single dose intravenous	- Group 1: 100% - Group 2: 100% - Group 3: 100% - Group 4: 82%	Functional X-ray and TC 3-D, blind valuation of bone at the intertransverse level
Zoledronate Tu et al.[27]	64 patients with OP and lumbar degenerative spondylolisthesis operated of intersomatic fusion	- Zoledronate, 5 mg IV (n=32) - Control group (n=32)	3 *postoperatio* days and then once a year	- Zoledronate: 1.75% - Control group: 2.56%	Independent evaluator x-ray. Fusion = absence of radiolucency around the graft, evidence of bony bridges between the intervertebral plates and absence of movement in the dynamic X-ray
Zolendronate Chen et al.[28]	79 patients with 1-level degenerative spondylolisthesis	- Zoledronate, 5 mg - Control with solution infusion saline	3 days after surgery Zoledronic acid (5 mg) or saline	Grade A or B more frequent in the zoledronate group at 3, 6, and 9 months compared with the control group ($p < 0.05$). Without being at 12 months	3 categories: - Grade A: complete bone bridges between both spinal bodies - Grade B: bone bridges in the upper or lower plate - Grade C: incomplete bone bridges (g) Fusion = angular movement less than 5° and Degrees A or B
Teriparatida Ohtori et al. (2012)[29]	57 women with OP and degenerative spondylolisthesis of 1 or 2 levels and instrumentation with fusion posterolateral with local graft	- Teriparatide (20 mg/day, injection subcutaneous) - Risedronate (17.5 mg/week, oral)	2 months before and 8 months after surgery (10 months in total)	- Teriparatide: 84% (X-ray) and 82% (CT) - Risedronate: 74% (RX) and 68% (TC) ($p < 0.05$)	X-ray and CT interpreted blindly by 3 surgeons. Definition of bony bridges between the saucers intervertebral and intertransverse
Teriparatida Ohtori et al. (2013)[30]	62 women with OP and degenerative spondylolisthesis	- Teriparatide (20 mg/day, SC) - Risedronate (2.5 mg/day, oral) - Control group	2 months before and 10 after surgery	Loosening of screws: - Teriparatide: 7% -13%; - Risedronate: 13% -26% - Control: 15% -25% ($p<0.05$)	X-ray and CT interpreted with blinding by 3 surgeons for assessing screw loosening

OP: osteoporosis; PLIF: posterior lumbar intersomatic fusion; X-ray: radiography; CT: computed tomography; 3-D: three-dimensional.

In a more recent study, also by Ohtori et al.[30], the effect of teriparatide and risedronate on the incidence of loosening of pedicle screws in patients operated on instrumented posterolateral fusion with local bone graft, specifically in 62 women with degenerative spondylolisthesis and osteroporosis. There was a statistically significant difference in favor of the teriparatide group in the loosening of screws (7-13%) compared with risedronate and the control group (15-26%).

Surgical strategies in the treatment of osteoporotic patients

Given the impact of osteoporosis on spinal fusion interventions, techniques have been developed that can increase the chances of successful vertebral fusion surgery.

In developing these strategies, it is essential to consider the most common forms of instrumentation failure discussed in the previous section[1]. These techniques are:

1. Methods that reinforce the segmental vertebral instrumentation

Increase of fixation points. The most common method is to extend the instrumentation with pedicle screws at least 3 levels rostrally and caudally to the compromised level. In this way the stress that is transmitted to several fixation points is reduced; This is especially important in patients over 65 with deformity or osteoporosis[10].

Reports suggest that the addition of wires or sublaminar hooks to the pedicle screws, that is to say hybrid assemblies, can significantly improve the results of an arthrodesis in the osteoporotic spine[31]. Although this technique is an effective option, it has not been widely used, probably due to the technical difficulties involved.

Use of cross-link connector. This has been shown that the addition of a transverse connector to the instrumentation with segmental pedicle screws increases the rigidity of the system and prevents the axial rotation of the instrumentation[32]. It has also been shown that they increase the resistance to extraction or pullout of the pedicle screws. However, this effect was substantially lower in the osteoporotic column[33].

2. Technical modifications in the placement of screws

Pilot hole size. The creation of a pilot hole is the first step for the insertion of a pedicle screw. It is important to take into account the size of the pilot hole, especially in the osteoporotic bone, since large pilot holes lead to poor grip of the screws, while very small pilot holes can increase the insertion torque, with the consequent risk of pedicle fracture.

Battula et al.[34] attempted to characterize the optimal size of the pilot orifice in the osteoporotic bone. Based on their results, the authors recommend the creation of a pilot hole no larger than 71.5% of the outer diameter for maximum resistance to pullout and minimize iatrogenic fracture of the pedicle, for which a more precise technique is required through high-speed milling, or the use of a punch instead of a gouge.

Preparation of the screw path. Under normal conditions, tapping improves the insertion path of the pedicle screws; however, the tapping influences the grip strength of the pedicle screws in the osteoporotic column.

Halvorson et al.[35] found that the lack of tapping or tapping with diameters below 1 mm of the final diameter of the screw, led to a greater grip strength of the pedicle screw.

Carmouche et al.[36] observed similar results in a study performed on corpses with osteoporotic bone: the tapping with the same diameter of the inserted screw led to a decrease in the pull resistance of the lumbar pedicle screw. On the other hand, the non-tapping or tapping with a lower diameter showed a greater force required for the extraction of the lumbar pedicle screws, although these differences were not replicated with the thoracic pedicle screws.

Bi-cortical fixation of pedicle screws. As it is known, the cortex of the vertebral body is significantly stronger compared to cancellous bone, so that the bi-cortical attachment or hook is stronger than the insertion in the spongy and uni-cortical. However, the bi-cortical fixation technique leads to an additional risk of injury to neurological structures, including the lumbar roots and the sacral sympathetic trunk; in vascular structures, such as the aorta and the vena cava; and in the colon[37].

Fixation with bi-cortical screws is usually carried out ventrally or cranially to the superior plate of S1, where the risk of damaging neurovascular structures is lower. It has been demonstrated that the latter technique significantly increases the torsional force and the extraction of the screw after a cyclic load compared with traditional anteromedially directed fixation[38].

The screws in S1 can also be inserted in what is known as a tricortical trajectory pointing towards the apex of the sacral promontory, so that the screw is inserted or meshed in the posterior cortex and anterosuperior of the superior plate of S1.

Hubbing involves inserting the screw to the head that is embedded or abutted with the dorsal cortical bone of the vertebra, theoretically avoids the windshield-wiper effect of the instrumentation system. However, in a cadaveric biomechanical study of this technique, Paik et al.[39] observed that hubbing led to a reduction of more than 40% in the screw's extraction force, regardless of BMD, so it was not recommended.

The cortical bone screw is an alternative trajectory of the pedicle screw. The insertion of the pedicle screws with the traditional trajectory from dorsolateral to ventromedial usually implies that the screw thread is located in the cancellous bone of the vertebral body, which in osteoporotic patients may cause poor anchoring. An alternative trajectory introduced in 2009 is the placement of the screw with a dorsomedial to ventrolateral trajectory, in order to couple the screw with more cortical bone of the pars interarticular and of the pedicle[40].

Although the trajectory of the screws placed with the cortical bone tends to be smaller in diameter and shorter in length compared to traditional techniques, it has a reportedly greater insertion torque and a greater extraction force of the screws[41].

Currently, there is only one randomized clinical trial that compared screws in cortical bone with the standard technique[42]. At 12 months, the fusion rates evaluated by computerized tomography were similar between the 2 groups (89.5%, n=39, in the conventional pedicle screw group and 92.1%, n=38, in the group of cortical screw), with no differences in pain relief in the leg or scores in the Oswestry disability index. However, subjects subjected to a cortical screw trajectory showed less blood loss, shorter surgical time, and a shorter incision length compared to their counterparts of conventional pedicle screws, probably due to the lack of need to expose beyond the facet joint at the screw insertion points.

3. Modification in pedicle screw design

Increase in the size of the screws. One of the fundamental techniques is the selection of longer instrumentation screws with a larger diameter. It is believed that the larger diameter screws "fill" more the pedicle and allow a better contact of the screw thread with cortical pedicle. In addition to providing a greater surface area of bone in contact with the screw thread and obtain an additional improvement in fixation, particularly in the sacrum. There are several studies that have confirmed that increasing the diameter and length of the screw improve the retention force of the screws[43,44].

Tapered pedicle screws. Changes in the design of the screws have also been considered in terms of morphology and screw threading. The use of conical screws, both with the conical thread and with the center or conical core, are common. If the outside diameter is constant, then the conical core allows a greater contact surface with the thread of the screw in the spongy vertebral body, where the osteoporotic bone has little retention power[45]. Screws with a cylindrical outer diameter and conical internal diameter demonstrate a better extraction force compared to other designs.

Cemented screws. One technique that has received considerable attention in recent years is the reinforcement of the pedicle screws through a cement layer or mantle around the screw at the level of the vertebral body. This apparently distributes the tension of the adjacent trabecular bone so that the screws are less prone to loosening or pullout[46] (Figure 3).

This effect was demonstrated more thoroughly with the use of polymethyl methacrylate (PMMA)[47]: there is an increase of between 2 to 5 times the force of screw extraction in the osteoporotic vertebrae, a repeated finding in many studies. In the same way, other bioactive cements constituted by calcium sulphate or calcium phosphate have been used with good results[48].

There is a growing experience in the cementation techniques of pedicular screws, and studies on its safety and efficacy have recently been reported and summarized in table 2.

On the other hand, this technique involves risks derived from the use of cement. The main ones are cement extravasation at the venous level, with the consequent possibility of embolism, and extravasation in the spinal canal, with risk of neurological injury. Fortunately, the vast majority of complications are infrequent or asymptomatic[49].

Expandable pedicular screws. Various modifications have been tested in the design of screws for osteoporotic spinal fixation; These include expandable screws and hydroxyapatite-coated screws. The expandable screws have a mechanism that allows the expansion of a part of the screw that is inside the vertebral body, keeping the part of the pedicle intact (Figure 3). The screw compresses the cancellous bone in the vertebral body as it expands, increasing the density of the bone around the screw. It has been possible to improve the pedicle fixation with a 50% increase in the resistance to the extraction of the screw in the osteoporotic bone[50]. This effect was magnified when the expandable screw was reinforced with bone cement[51,52]. One drawback of this technique is the difficulty involved in revision surgeries that require removing expandable screws.

4. Strategies for the prevention of "proximal joint kyphosis" (PJK)

Regarding PJK prevention strategies, there is no clearly effective solution. Pre-operative assessment of bone mass density is essential and timely correction is possible. Other strategies related to the surgical technique are: the adequate curving of the terminal bar in kyphosis, the placement of hooks in the transverse processes of the superior vertebra of the instrumentation, and the avoidance of finishing the instrumentation in a kyphotic vertebral segment. Minor correction of kyphosis is important but also maintaining an adequate sagittal and coronal balance.

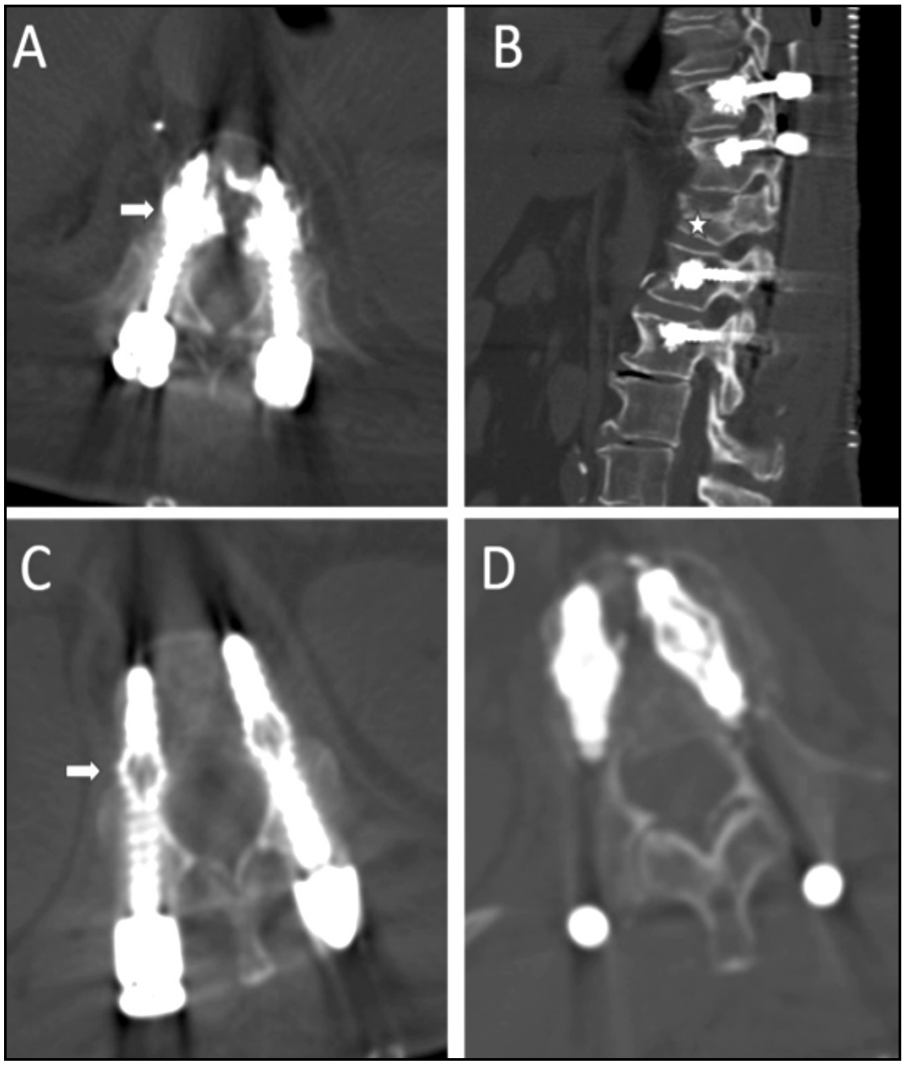
Most authors advocate vertebroplasty at one or two levels higher than the instrumentation to avoid fracture or vertebral collapse in this susceptible segment. Table 3 summarizes the main surgical strategies in the osteoporotic column.

Spinal reinforcement techniques

Vertebroplasty and kyphoplasty are therapeutic procedures that can be included within the so-called "spinal reinforcement techniques" and that are carried out by interventional radiologists, by traumatologists or by neurosurgeons, percutaneously, usually with transpedicular approach. Percutaneous vertebroplasty involves introducing a bone cement, such as polymethylmethacrylate (PMMA), in a fractured vertebral body, to relieve pain by reinforcing and stabilizing the vertebral fracture (Figure 4). Similar to vertebroplasty, in percutaneous kyphoplasty, prior to the administration of cement at the level of the fractured vertebra, a balloon is inserted that is inflated to restore the height of the vertebral body and reduce kyphotic deformity. When the balloon is removed, a cavity or nest remains inside the vertebral body, allowing the cement to be introduced at a lower pressure and with a higher viscosity, which reduces the risk of extravasation. Some authors prefer to call kyphoplasty "balloon vertebroplasty"[53].

As has been amply demonstrated in the literature and as it has been assured by different scientific societies, the use of vertebroplasty or kyphoplasty is a safe, effective and lasting procedure in selected

Figure 3. (A) CT axial cut and (B) sagittal pedicular screws are observed with the technique of vertebral reinforcement with cement. (C) and (D) Axial axial CT shows the technique with expandable screws, with part of the expanded screw at the level of the vertebral body (arrow)



patients with symptomatic osteoporotic and neoplastic fractures, as long as it is carried out according to published standards. These procedures must be offered when non-surgical medical treatment has not provided adequate pain relief and this is significantly altering the quality of life of the patient[54].

Multiple case series, retrospective and nonrandomized prospective studies and, more recently, randomized controlled trials, have shown how these techniques achieve statistically significant improvements in pain and function, particularly in ambulation, with respect to medical treatment[54].

There are currently a total of six randomized controlled trials, including a total of 842 patients, in which the vertebral reinforcement treatment, vertebroplasty or kyphoplasty, is compared with medical or simulated non-surgical treatment in osteoporotic vertebral fractures[54] (Table 4).

The two randomized controlled trials with the largest number of patients studied have shown benefits for vertebroplasty and kyphoplasty that last up to 1 year after the intervention[55,56]. Supporting these results, another study showed significant benefits for vertebroplasty that persisted up to 3 years after treatment[57]. On the other hand, other investigations have reported benefits of vertebroplasty up to 1 month after intervention, but not beyond this point[58,61]. The INVEST clinical trial showed a very significant trend towards clinical improvement in relation to pain for the group treated by vertebroplasty at the first month of treatment, despite the fact that no statistically significant differences were achieved[59]. On the other hand, only one study failed to demonstrate that vertebroplasty treatment was beneficial after the first month after surgery[60]. Therefore, based on these studies, we may conclude that vertebral reinforcement treatments in osteoporotic vertebral fractures are clearly beneficial in the short term and probably also in the long term[54] (Table 4).

Conclusions

The progressive aging of the population has significantly increased the procedures of spinal fusion. The prevalence of osteoporosis in patients who undergo surgery ranges to around 50% in women over 50 years of age. A significant proportion of these patients are not adequately diagnosed with osteoporosis or vitamin D deficiency and, therefore, receive no timely treatment. There is evidence that patients with osteoporosis and with uncorrected hypovitaminosis D have worse results in cervical and lumbar disability scales. Patients with osteoporosis, having a poor bone mineral density, suffer from worse rates of bone fusion in spine arthrodesis.

Surgical complications are more frequent in patients with osteoporosis, especially in those who do not receive timely treatment and the relevant surgical technique modifications are not made.

Currently, a variety of pharmacological and surgical medical treatment strategies are available that can improve clinical outcomes and fusion rates of patients undergoing spinal fusion.

Table 2. Studies that assess the effect of different surgical techniques in patients with osteoporosis

	Patients	Technique surgical	Rates of fusion	Methods of fusion rating
Cannulated and cemented screws				
Moon et al.[22]	37 patients with OP and spinal canal stenosis degenerative	Cannulated and cemented screws with PMMA	91.9%	X-ray with intersomatic bony bridges, absence of movements in functional studies, absence of radiolucent pattern
Piñera et al.[22]	23 patients with OP >70 years, lumbar spondylolisthesis degenerative and instability or lumbar stenosis	Instrumentation of cannulated screws and cemented with PMMA	- 74% (X-ray) - 100% (CT after 6 months) - Radiolucentity at the interface cement screw in 3 patients	X-ray with intersomatic bony bridges CT bony bridges intertransverso or interfacetario
Dai et al.[22]	43 patients with OP and degenerative illness spinal	Instrumentation of cannulated and cemented screws	100%	CT in 2- and 3-D using the methods of Sapkas' and Christiansen's
Expandable pedicle screws				
Cook et al.[51]	145 patients studied; 21 had OP	Expandable pedicle screws (Omega21 spinal system)	86%	X-ray demonstrating trabecular bone bridges between the fused segments
Gazzeri et al.[51]	10 patients with OP	Expandable pedicle screws (OsseoScrew)	0% screw loosening	X-ray and CT to assess radiolucency around screws
Wu et al.[51]	157 patients with stenosis of channel and OP	Expandable pedicle screws: n=80 Conventional screws: n=77	- Expandable: 92.5% - Conventional: 80.5% (p=0.048)	RX dynamics CT blindly evaluated by 2 radiologists. Fusion = trabecular bone through the fused segments. Translation <3 mm or angulation <5 mm in flexion-extension RX

OP: osteoporosis; PMMA: polymethylmethacrylate; X-ray: radiography; CT: computed tomography; 2-, 3-D: bi-tridemensional.

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Table 3. Surgical beads to maximize the results of spine surgery in patients with osteoporosis.

1. The prevention and timely treatment of osteoporosis is the most important principle.
2. Early assessment by the osteoporosis specialist for the preoperative optimization of osteoporosis.
3. Longer instrumentation assemblies to avoid starting or terminating the instrumentation in the cervicothoracic or thoracolumbar junction or in a kyphotic segment.
4. Include at least three fixation points above and below the vertex of the deformity.
5. Hybrid constructions (pedicle screws, hooks, wires) can improve strength. Fixing. Fixation with iliac and sacral screws in long fusion constructions is recommended, thus maximizing stability.
6. The support of previous column increases the distribution of load, decreases the tension in the instrumentations via later.
7. The direction of insertion of the pedicle screw affects the extraction force or pullout, so anchoring or grasping in the subchondral bone (eg, sacral promontory) is recommended to maximize fixation.
8. The tapping with lower diameter increases the insertion torque and the extraction force or pullout of the pedicle screw.
9. Avoid the hubbing of the pedicle screws since it negatively affects the extraction force or pullout.
10. The use of vertebral reinforcement techniques with cemented or expandable screws can improve the clinical radiological results.

Figure 4. MRI sequence T2 (A) and (B) T1: vertebral fracture is observed by acute compression at level D7 with vertebral body edema. (C) Lateral X-ray of the dorsal spine shows vertebral wedging at level D7 with discrete segmental kyphosis. (D) Vertebroplasty of the fractured level with improvement of segmental kyphosis. (E) Lateral X-ray of follow-up, refracture with vertebral collapse of D7 and a significant segmental kyphosis is observed. (F) Rescue surgery by arthrodesis with cemented pedicle screws from D5 to D9, with correction of kyphosis

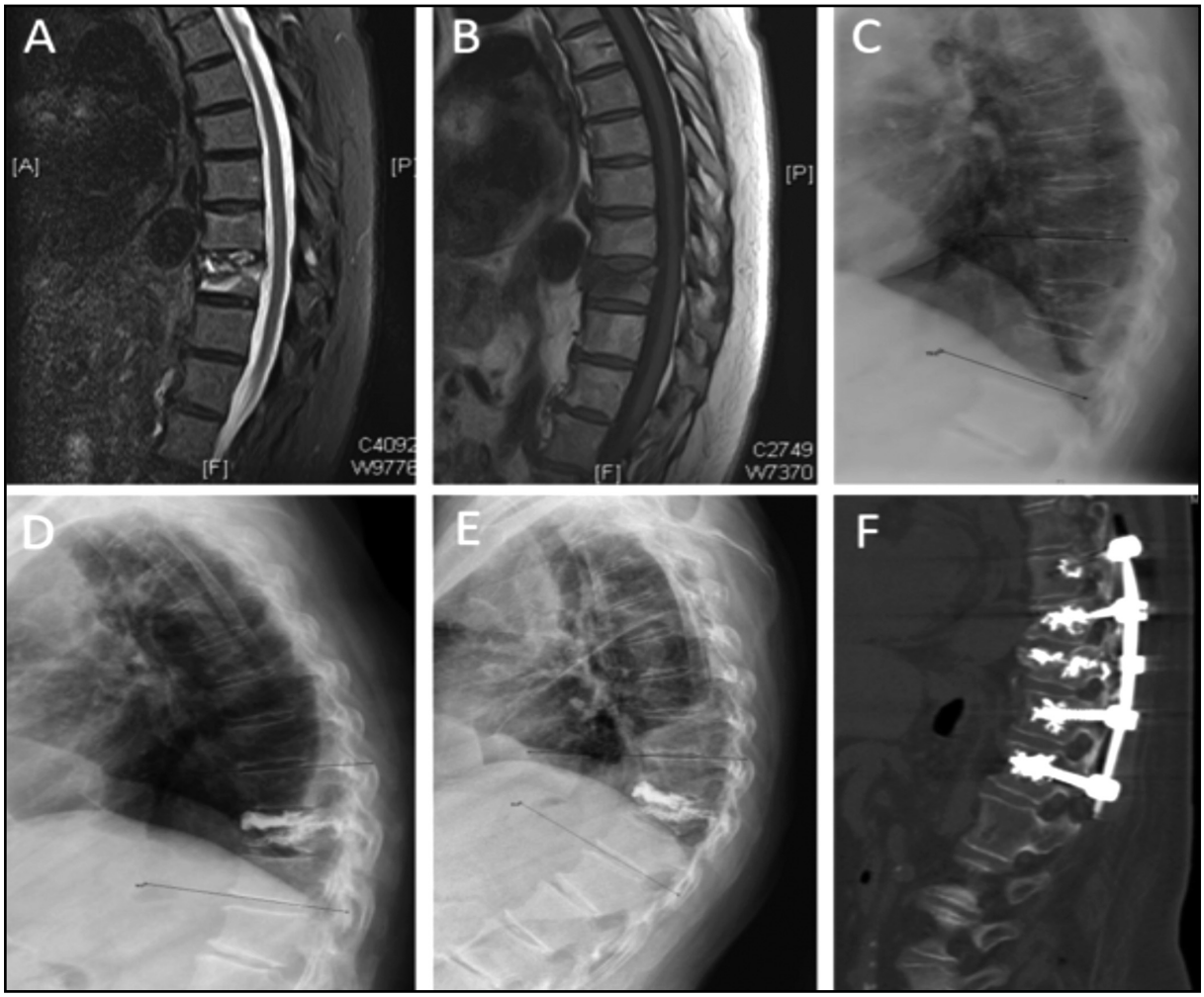

Table 4. Randomized controlled trials comparing vertebral reinforcement treatment, vertebroplasty or kyphoplasty, with medical or simulated non-surgical treatment, in osteoporotic vertebral fractures

RPCS	n	Inclusion criteria	Groups	Parameters	Tracking time	Results (in relation to the "vertebroplasty" group)
FREE (2009)	300	1-3 VFC; at least 1 with edema (MRI) and loss >15% of height; <3 months of the fracture	Kyphoplasty (n=149) vs medical treatment (n=151)	- Main: Short-Form-36 physical component summary (SF-36 PCS). - Secondary: pain back and disability	12 months	Significant clinical improvement at the first month (p<0.001). Significant clinical improvement in back pain and disability per year. No differences in relation to adverse effects.
INVEST (2012)	131	1-3 VFC; <12 months of fracture; Patients with malignant tumor pathology are excluded	Vertebroplasty (n=68) vs placebo (n=63)	*Modified Roland-Morris Disability Questionnaire (RDQ) and intensity of pain in the first month*	12 months	No significant differences in the primary parameters at the first month, although there were clinical differences in relation to pain intensity at the first month (p=0.06). No differences in relation to adverse effects
Buchbinder et al. (2009)	78	1-2 VFC; at least 1 with edema (MRI) or visible fracture line; <12 months of the fracture	Vertebroplasty (n=38) vs placebo (n=40)	General pain at 3 months	6 months	No significant differences between the groups at any time during the follow-up
Rousing et al. (2009 y 2010)	49	1-3 VFC; <8 months of fracture; Patients with malignant tumor pathology are excluded	Vertebroplasty (n=25) vs medical treatment (n=24)	- Main: intensity of the pain (VAS) at 3 and 12 months. - Secondary: scales functional	12 months	No significant differences in relation to pain or functional scales at 3 and 12 months. Significant differences in relation to pain at the first month (p<0.01)
VERTOS II (2010)	202	1-3 VFC; at least 1 with edema (MRI) and loss >15% of height; <6 months of fracture; Patients with malignant tumor pathology are excluded	Vertebroplasty (n=101) vs medical treatment (n=101)	- Main: intensity of the pain (VAS) to the first month and 12 months. - Secondary: analysis of cost effectiveness	12 months	Significant differences in relation to the intensity of pain at all times of follow-up, with an acceptable cost
Farrokhi et al. (2011)	82	1-4 VFC; vertebral edema (MRI); pain present between 4 weeks and 10 months; osteoporosis demonstrated by densitometry	Vertebroplasty vs medical treatment. Crossing was allowed from the group treated after the first month	Intensity of pain (VAS); Oswestry Disability Index; height of the vertebral body; degree of kyphosis	36 months	Significant improvement in relation to pain at all times after 6 months and in relation to the Oswestry Disability Index at all times after 3 years. Significant improvement at all times in relation to radiological parameters

RPCS: randomized and prospective controlled studies; VAS: Visual Analog Scale; VFC: vertebral fracture-compression; FREE: Fracture Reduction Evaluation Trial; INVEST: Investigational Vertebroplasty Safety and Efficacy Trial; MRI: magnetic resonance.

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Sant Joan d'Alacant Declaration defending Open Access to scientifc publications, from Publishing Group of Spanish Journals concerning Health Sciences (GERECS, from original title in Spanish)

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The concept of Open Access (OA) not only pertains to scientific documentation access, but also covers more or less restrictive reuse permissions based on reserved distribution rights. From this idea, several initiatives have sprung up, on a profit or non-profit basis, aimed at facilitating universal Internet access to scientific publications.

Projects such as Scientific Electronic Library Online (SciELO, 1998), The Scholarly Publishing and Academic Resources Coalition (SPARC, 1998), PubMed Central (PMC, 2000), The Public Library of Science (PLOS, 2000) and BioMed Central (BMC, 2001), pioneered a revolution that would reestablish commercial strategies for scientific publishing. Other sources include Dialnet (2001), *Red de Revistas Científicas de América Latina y el Caribe, España y Portugal* (Redalyc, 2003) and the Directory of Open Access Journals (DOAJ, 2003), would also spread the OA movement and facilitate the global knowledge process in the scientific communities throughout Latin America.

The first Declarations that set the bases for future OA development encompassed: the Budapest Open Access Initiative (2002), the Berlin Declaration on Open Access to Knowledge in the Sciences and Humanities, (2003) and Bethesda Statement on Open Access Publishing (2003). The latter is considered the declaration of principles for the health sciences.

Furthermore, declarations have been published, generally promoted in meetings of editors of scientific journals that recommended the proper development of open access to science. In Spain, we could cite the Declaration of the Alhambra (2010), which provided recommendations for the policies and an action plan for developing open access in southern Europe. More recently, in Latin America, the Declaration of the Meeting of Consortiums of Latin America and the Caribbean (2017) was drawn up, which among its recommendations discusses the movement away from Open Access with the growing emergence of paid journals for publication with prices that are sometimes abusive (APC, article processing charges) with the Open Access label.

The last Amsterdam conference, «Open Science – From Vision to Action» (2016) formulated two important pan-European objectives to be reached in the year 2020:

· Full open access for all scientific publications.

· A new approach oriented towards the optimal reuse of research data.

To achieve these objectives, applying new assessment and reward systems for scientific works and fomenting good practice policies were proposed.

In this line, ministers of science of the European Union nations agreed, in the session held on May 27, 2016, the document, The transition Towards an Open Science System - Council conclusions, recommending that the publications resulting from publicly-funded research be made available free of charge by 2020. To this end, each country must implement its own publication policy.

This agreement underscores that the principle for optimal reuse of research data should be "as open as possible, as closed as necessary." It also emphasizes that opportunities for the optimal reuse of research data can only be realized if data are consistent with the FAIR principles (findable, accessible, interoperable and re-usable) within a safe and reliable environment.

Thus, the European Open Science Policy Platform, at its third meeting in March 2017, adopted the following recommendations:

· The interested communities, the Member States and the European Commission should jointly assess and identify how the Open Access 2020 mandate should be achieved.

· Progress towards a complete OA should take into account the speed with which the publication system changes and how academic communications grow in richness and variety.

· There is no single solution, although the ultimate goal for all disciplines may be the same. Issues related to compliance, including incentives and enforcement, should be proposed, clarified and harmonized in a manner that is sensitive to all disciplines.

· The options of payment terms for the publication should be clear and easy to locate under the conditions established by each journal.

· As of 2020, the European Commission must move towards a broader definition of OA, which incorporates the full range of formats and emerging applications as a result of scientific research.

Taking into account all the aforementioned, aware of the future changes that the editors of the Spanish journals on health sciences will have to assume, they propose the following recommendations and requests:

1. Adhere to the criteria emanating from the March 2017 meeting of the European Open Science Policy Platform.

2. Encourage our institutions to support Expression of Interest OA 2020 (https://oa2020.org/) and, consequently, sign its principles.

3. Urge research agencies at the national level to implement scientific policies that require their researchers to deposit their publications in institutional repositories.

4. Take into account the social commitment of journals in OA with the accessibility of knowledge, including citizenship, the recognition as academic/professional merit is requested for publication in open access journals that are indexed in platforms committed to excellence, such as SciELO, Redalyc or DOAJ.

Also, in line with the San Francisco Declaration on Research Evaluation (San Francisco Declaration on Research Assessment, DORA, 2012), the editors of health sciences journals consider it necessary to support the adoption of the following practices:

1. Reduce the emphasis of the impact index, or other metrics based on indicators on the journal in which it was published, as a personal promotion tool.

2. Promote new indicators related to the scientific content of the article instead of metrics concerning the journal in which it was published.

In Sant Joan d'Alicante, on November 25, 2017

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- María Dolores Ruiz López. Editora de la revista *Ars Pharmaceutica*. Universidad de Granada. Granada (España).

- Manuel Amezcua Martínez. Director de la revista Index de Enfermería. Fundación Index. Granada (España).

- Carlos Álvarez-Dardet. Director de la revista Gaceta Sanitaria. Sociedad Española de Salud Pública (SESPAS). Barcelona (España).

- Mikel Astrain Gallart. Director de la revista Dynamis. Universidad de Granada. Granada (España).

- María del Mar Vaquero Pérez. Directora de la revista Cirugía Plástica Ibero-Latinoamericana. Federación Ibero-latinoamericana de Cirugía Plástica (FILACP) y Sociedad Española de Cirugía Plástica, Reparadora y Estética (SECPRE). Madrid (España).

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