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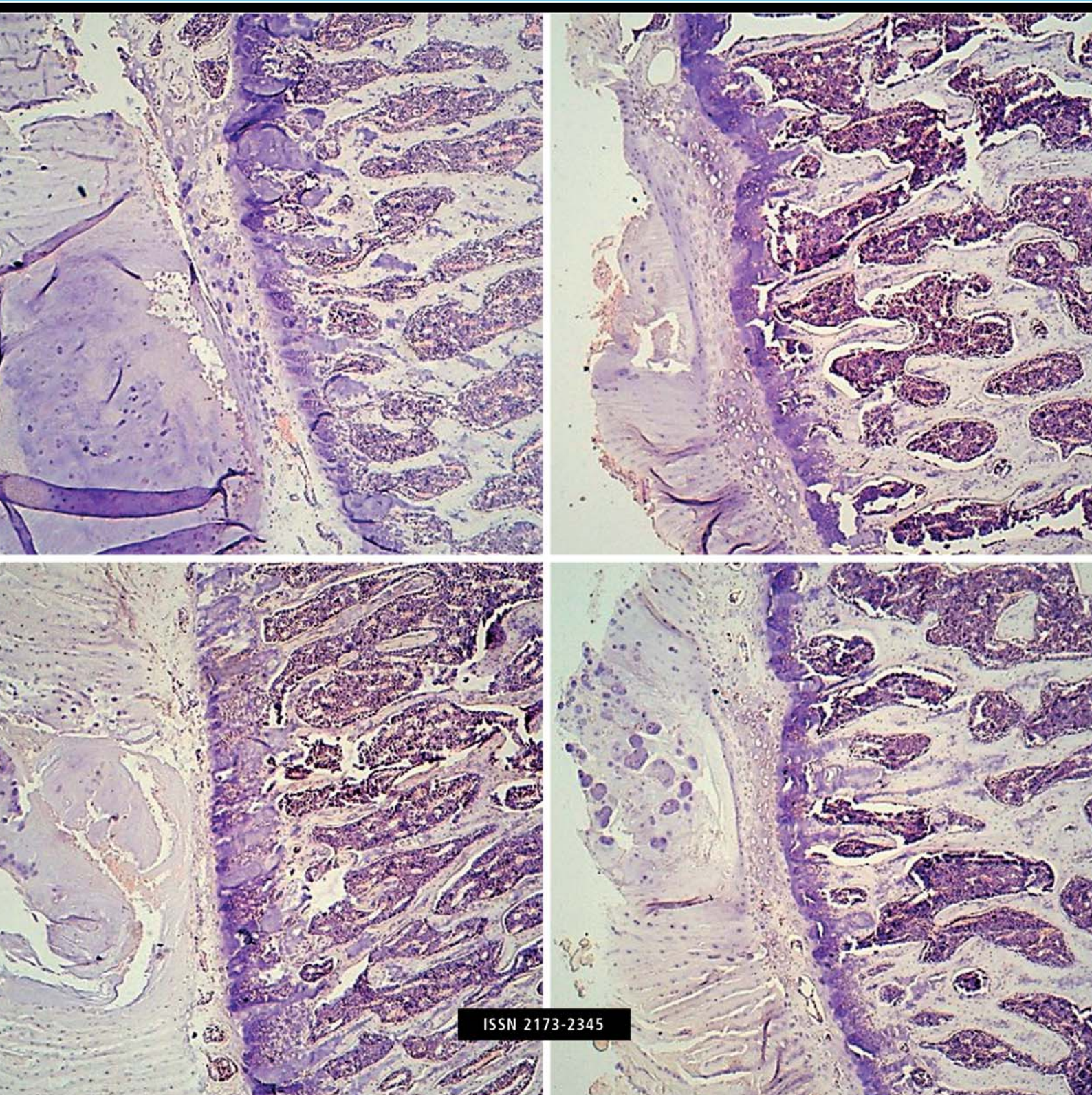

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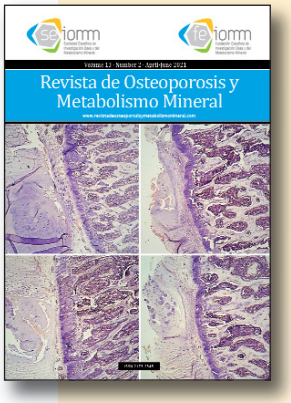

Our cover: 100X hematoxylin eosin staining. Trabecular components of the L4 vertebra in SHAM, orchidectomized, OPG-Fc-treated orchidectomized, and testosterone-treated orchidectomized rats.
Author: Concepción de la Piedra Gordo. Research Biochemistry Department. Institute of Medical Research, Jiménez Díaz Foundation. Madrid (Spain).

Summary

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Sociedad Española de Investigación Ósea y del Metabolismo Mineral

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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.

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Farewell

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Gómez de Tejada Romero MJ, Sosa Henríquez M
Steering Committee of the Journal of Osteoporosis and Mineral Metabolism

The Journal of Osteoporosis and Mineral Metabolism (ROMM) was created at the end of 2009 and was presented at the Congress of the Spanish Society for Bone Research (SEIOMM) that year, held in Santander. We have participated from the beginning, both in its creation, start-up and later development, until today. It is the SEIOMM associates who should assess our management. For our part, we believe that a cycle has been completed and that the renewal of the management team is appropriate. For this reason and through this editorial, we say farewell, thanking all those who have trusted and collaborated with us: boards of directors, members of the editorial committee and associates, some who have submitted articles and others who have served as reviewers. A special thanks to our collaborators on a day-to-day basis: Jesús and Concha, publishers of Ibáñez y Plaza; Gabriel Plaza, responsible for the website; and David Shea, translator of the journal, with whom it has always been so easy to work, and who with professionalism and dedication have contributed enormously to make this journal where it is right now. Thank you all.

In a previous article, recalling the first ten years of the journal, we reviewed the creation process and its beginnings[1], a function that we believe has been fulfilled, without a doubt, with the consolidation of the magazine. The ROMM has been and continues to be the vehicle for publishing the communications presented to the annual Congresses of the SEIOMM. Another function, more debatable, is to serve as a means for associates to publish part of their research, ensuring that it is increasingly disseminated. We say debatable, because after 12 years at the helm of the journal, we think that the associates, in general, believe that it is unnecessary.

We have tried to ensure, on the one hand, that the ROMM is present in the largest number of databases, repositories and Web pages. Furthermore, to see that the quality of the articles published improves. If we take as a reference different tools dedicated to assessing both aspects, it would seem that both tasks have been fulfilled, with the presence in important databases such as Scopus, Google Academic and others such as ERIHPLUS and MIAR[2,3], in addition to obtaining an index of impact.

Where are we listed? Databases, directories and repositories where the ROMM is included

ROMM is currently included in the following databases and repositories: Scopus, Web of Sciences, SciELO, DOAJ, ERIHPLUS, Redalyc, IBECS, Embase, Open J-Gate, Free Medical Journals, American Society for Scientific Research (SIIC), Google Scholar, Medes, ÄZ3, e-magazine@s, WorldCat, Latindex, EBSCO, Medic Latina, Dialnet, Safetylit, Mosby´s, Emcare, Academic Keys, CRUE, Hinari, REDIB, Emerging Sources Citation Index, British Library, ROAD and MIAR, a total of 31 databases.

Some of these databases feed back to each other, as is the case with DOAJ, SciELO and Dialnet. Whilst they are all important and without detracting from any of them, SciELO is widely established among Spanish and Portuguese-speaking countries, Redalyc covers mainly Spanish-American countries, especially Mexico, and Scopus is after Journal of Citation Reports, the most popular database used with its own "impact factor" which we will refer to later. Finally, Google Academic is becoming in recent years as a place to search for scientific articles complementary to PubMed, since all the articles that are collected in PubMed are also included in Google Academic, but the reverse is not the case.

There are two databases in which, due to their rigor, it has been especially difficult to be included. They are ERIHPLUS, a Norwegian database that rejects almost half of the applications[2] and the University of Barcelona's Information Matrix for Journal Analysis (MIAR, from Spanish acronym), which in turn collects information from 116 databases, rating journal quality. In the field of osteoporosis, ROMM is in the middle of the table[3], with a score of 9.6 out of a possible maximum of 11 (see tables 1 and 2). In the Academic Google, within the Spanish magazines, the ROMM is located in position 71 of 99[4].

Table 1. MIAR score of journals related to bone mineral metabolism (2021)

Name	Ranking MIAR (ICDS)
New England Journal of Medicine	11
Osteoporosis International	11
Journal of Bone and Mineral Research	11
Bone	11
Journal of Bone and Mineral Metabolism	11
Current Osteoporosis Reports	10,8
Archives of Osteoporosis	10,7
Clinical Reviews in Bone and Mineral Metabolism	9,8
Revista de Osteoporosis y Metabolismo Mineral	**9,6**
Journal of Osteoporosis	9,5
Bone Reports	9,3
International Journal of Osteoporosis and Metabolic Disorders	4,1

Evolution of ROMM in Scopus

Included in the Scopus database, after three attempts, the ROMM had for the first time an "impact factor", the one calculated by Scopus, which is the so-called Scimago Journal Rank or SJR. The first year that SJR had, in 2015 it was 0.108. It has been increasing on a yearly basis, currently attaining 0.133 in 2020 (see figure 1)[5]. We are in the 4th quartile (Q4), in the area of Endocrinology, Diabetes and Metabolism, which is where the journals dedicated to bone mineral metabolism are included. We are ranked 195 out of a total of 232 magazines[6].

The road to the Journal of Citation Reports (JCR) and PubMed

From the beginning, our goal has been the inclusion of ROMM in the JCR and with it, immediately in PubMed. It is the most prestigious database and despite the existence of other "impact factors" such as Scopus or even Google Scholar[4-6], it is the impact factor par excellence.

Figure 1. Evolution of the impact factor of the ROMM with Scopus (called SJR)[5]

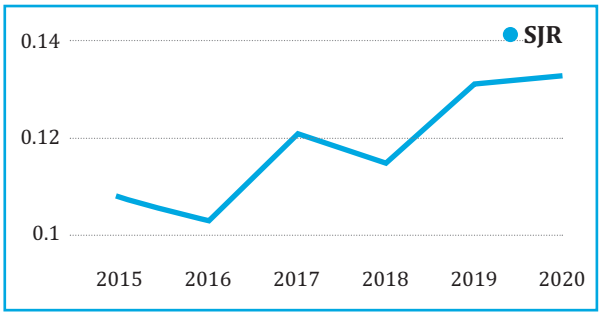

Table 2. Evolution of MIAR's valuation of ROMM

2016	2017	2018	2019	2020
9.3	9.4	9.5	9.5	9.5

We have twice requested the inclusion of the journal in the JCR, and on both occasions were rejected. Some reasons for this rejection could be debated, because they are based on opinions, and others could even be refuted, but the basis for the refusal to be included is undeniable: it is a home-based journal, in which authors, reviewers and editorial committee are repeated over and over again. Another reason they put forward is that the articles, in general, are not of sufficient quality. This reasoning is based on the limited impact they have in other scientific journals.

These drawbacks are difficult to solve. The journal has had a permanent shortage of articles since its creation. Completing each issue is a struggle. The request for quality originals from SEIOMM researchers is a constant, both from the SEIOMM website, and in corporate emails sent to associates by the Board of Directors, and finally, individually, from the Director to the SEIOMM researchers. However, the main source of original articles sent to the journal are those that are required to remedy a debt contracted by a research group when one of its members accesses a FEIOMM grant, either for research or to attend Congress. American Bone Mineral Metabolism (ASBMR). Therefore, the articles are sent as part of a "contract" and thus cover a need to continue to be eligible for future scholarships. They are, therefore, on many occasions, articles that constitute the remnants of an investigation whose original production was sent to a journal with an impact factor of the JCR, which on the other hand is reasonable and with which the ROMM cannot compete. Thus, the articles that we publish are not the best generated by each research group and for that same reason they are not referenced, with which the scientific repercussion of them in other journals will be low and this will make a good evaluation by the ROMM difficult. among JCR reviewers. Thus the vicious circle is closed.

What is the future of ROMM? what do SEIOMM members want from the journal?

The future of ROMM will be that which its members decide, but through their actions, which must require sending in quality publications, especially original ones. The more or less public manifestations of "unconditional support" for the journal will be of no use if this is not translated into facts: on the one hand, the sending of quality originals and, on the other, in collaboration as reviewers.

This is an enormous difficulty that we have encountered. Very few SEIOMM associates agree to review an article submitted to the journal, despite the fact that in the selection of said reviewer we take into account that the article that we request that they evaluate is from their usual area of work and/or research. On the contrary, for each review request that is accepted by the expert, we obtain an average of three rejections and this among those who respond to the email in which the review is requested. The absence of a response is not uncommon, in mail duly verified as correct. Other times, we observe that the review is written in a rapid, inconsistent way, lacking detail and documentation. Therefore, it does not help at all. At times, we have had to resort to personal favor to get a review.

The journal now enters a watershed moment. With an additional push from the new leadership team, perhaps the JCR evaluation could be requested within 3 years and it could be achieved. But we consider that we have completed a cycle and that we must make way for others who, with courage and enthusiasm (which we have exhausted), complete the task. Not only do we want it, but to the best of our ability we are unconditionally willing to collaborate in this endeavor.

We would like to conclude by extending our thanks to Manuel Naves Díaz, current SEIOMM President, in particular, for his sincere, total commitment to the journal and we wish him all the best.

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Impact of dementia on the survival of patients with hip fracture after undergoing total and partial prosthesis

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Summary

Objetive: To carry out a comparative survival analysis of patients diagnosed with hip fractures (HF) in the Basque Health Service from 2010 to 2016 depending on whether or not they were diagnosed with dementia and the type of arthroplasty.

Material and methods: Observational study (real world data) of survival. The data were obtained from the administrative and clinical databases of the Basque Health Service using the Oracle Business Intelligence (OBI) manager. All cases of femur neck fractures from 2010 to 2016 were analyzed in the Basque Health Service. A descriptive analysis was carried out to detect differences between groups according to previous diagnosis of dementia and type of prosthesis. The Kaplan-Meier method was used to obtain the survival curves and their comparison was made in pairs using the Achievement test. The adjusted risk of death for each group was analyzed with the Cox regression model.

Results: 5,867 patients with CF were identified, being 1,131 patients without dementia and total prosthesis, 3,073 without dementia and partial prosthesis, 176 with dementia and total prosthesis and 1,487 with dementia and partial prosthesis. The median survival was 9.08 years, 3.79 years, 2.55 years, and 2.54 years respectively. The comparison of the survival curves was significant for all cases except between the last two groups. Using the first group as a reference, the odds ratio of death for the rest was 1.56, 2.27 and 2.37 respectively. When analyzing the risk of death only for patients with dementia, the type of prosthesis was not statistically significant.

Conclusions: Dementia influences the survival curve of patients who undergo arthroplasty after a femur neck fracture, with those who undergo a total arthroplasty have a similar mortality rate as those who undergo partial arthroplasty.

Key words: dementia, hip fractura, arthroplasty, Cox regression.

Introduction

Hip fractures represent a general public health problem due to their high incidence and their impact on mortality and loss of quality of life[1]. In the coming years, with the progressive aging of the population, its incidence is expected to increase, incurring a significant drain on resources[2]. Crude mortality figures after a hip fracture are considered in most studies. An estimated 5% of patients die in-hospital and approximately 20% do so during the first year, depending on the series[3]. However, hip fractures occur in elderly patients who have an associated comorbidity that also influences their survival[4]. The highest mortality rates are reported mainly in the elderly, sick or disabled populations[5]. A recent meta-analysis exploring the magnitude and duration of the excess risk of mortality after hip fracture found the highest risk in the first 3 months after the fracture, and mortality remained high even after 10 years[6]. Excess risk increases with age and, at any age, is higher for men than for women[6].

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Dementia affected 6.53% of the Spanish population over 60 years of age in 2020[7]. The current prevalence worldwide is more than 40 million patients, which will double every 20 years[8,9]. Patients with dementia have an increased risk of suffering a hip fracture and also evolve significantly worse than patients without it due to higher mortality[3]. They tend to be patients with an increased risk of hip fracture due to their older age, significant comorbidities, polypharmacy, limited mobility, and a tendency to fall[4,10]. Treatment options for hip fracture in general include total prosthesis, partial prosthesis, osteosynthesis and conservative treatment without surgery, but in patients with dementia the results are usually worse, with a higher rate of postoperative complications and medium term[5], so the choice of treatment should be based on these clinical considerations.

Our study aimed to analyze the comparative survival of patients diagnosed with hip fractures (HF) who underwent arthroplasty in the Basque Health Service from 2010 to 2016 depending on whether or not they were diagnosed with dementia and the type of joint replacement, total and partial.

Material and methods

Design

A retrospective and observational study (real world data) was carried out on the survival of hip fracture cases registered in the Basque Health Service (SVS). The necessary data were obtained anonymized from the SVS administrative and clinical databases using the Oracle Business Intelligence (OBI) manager. The electronic medical record is fully implemented in the public health system of the Basque Country and associated with administrative data of the patient. This allows each of the contacts and all the use of resources of the patients with the health system to be registered. The clinical research ethics committee of the Basque Country approved the study protocol on February 14, 2019 with registration number PI2019010. Informed consent is not required as the database is anonymized.

Patient sample and variables

All cases of femoral neck fractures operated on by partial or total prosthesis from 2010 to 2016 were analyzed in the Basque Health Service. The diagnosis of femoral neck fracture included ICD-9 codes 820.0 and ICD-10 codes S72.0. The surgical procedures included the ICD-9-CM codes 81.51 for the total prosthesis and 81.52 for the partial one. Within this population, patients with a previous diagnosis of dementia were identified both at the primary care level, as well as at the level of hospital care, emergencies, home care or hospitalization and / or outpatient specialist consultations with a validated procedure[11]. Diagnosis of dementia included ICD9-MC codes 290, 294.1, and 331, as well as ICD10 codes F01.5, F02.8, F03.9, F05, G30, and G31. The identification of dementia also included the prescription of specific drugs for Alzheimer's disease identified with the ATC code N06D. The final date of follow-up was set at October 31, 2020. The following variables were obtained for each patient: age, sex, risk index from the American Society of Anesthesiologists (ASA), diagnosis and date of dementia, diagnosis and date of hip fracture, type of prosthesis, vital status at the end of follow-up and date of death in such cases. The ASA risk index was used as an adjustment co-variate for the presence of comorbidities and appears in the database as assigned by the anesthetist responsible for the intervention.

Statistic analysis

Statistic analysis was carried out using the R statistics program (version 3.3.2) with a confidence level of 95%. First, a univariate descriptive analysis was performed to detect differences between groups according to a previous diagnosis of dementia. Fisher's exact test was applied for categorical variables of two categories and expected value less than or equal to 5. In the case of continuous variables with normal distribution, the comparison of means was carried out using the Student's t test.

Subsequently, a survival analysis was carried out that included the non-parametric methods of Kaplan-Meier and Cox to compare survival adjusted for previous diagnosis of dementia and type of prosthesis. Four groups were differentiated: 1) patients without dementia and total prosthesis, 2) patients without dementia and partial prosthesis, 3) patients with dementia and total prosthesis, and 4) patients with dementia and partial prosthesis. For each group, the survival functions and curves were calculated using the Kaplan-Meier method, which calculates the cumulative survival ratio at the individual level of each patient. For the comparison of the survival curves, the Mantel-Cox test, also known as the achievement test, was used. The survival curves were compared in pairs. Using Cox regression, the risk of death was analyzed as a function of time, adjusting for age, sex, ASA risk and group (defined based on the previous diagnosis of dementia and type of prosthesis). This calculation was repeated exclusively for the subgroup of patients with dementia, adjusting this time for age, sex, ASA risk index and type of prosthesis.

Results

Between 2010 and 2016, 5,867 patients diagnosed with a femoral neck fracture were identified, of which 1,663 had a previous diagnosis of dementia. As can be seen in table 1, the mean follow-up was 2.98 years for patients with dementia and 4.29 years for patients without dementia, while the mean age was 84.71 years and 81.91 years respectively. In the univariate analysis, significant differences were observed by age, sex, ASA risk and type of prosthesis. In the group of patients with dementia, there was a higher percentage of partial dentures, as well as a higher ASA risk. There were also significant differences in the mortality rate, since it was higher in the group of patients with a previous diagnosis of dementia (82.4%) than in the rest (63.5%).

Figures 1 and 2 show the survival curves obtained using the Kaplan-Meier method, the first being differentiated only by a previous diagnosis of dementia and the second by a previous diagnosis of dementia and type of prosthesis. Of the 5,867 patients in the total sample, 1,131 were patients without dementia and with total prosthesis, 3,073 patients without dementia and with partial prosthesis, 176 patients with dementia and total prosthesis, and 1,487 patients with dementia and partial prosthesis. The follow-up that indicated the probability of survival at 50% for each subgroup was 9.08 years, 3.79 years, 2.55 years and 2.54 years respectively (Table 2 and Figure 2). Table 3 shows the log-rank test that compared the survival curves of the four groups. Significant differences were observed between the curves of all groups, except between the curve of the group of patients with dementia and total prosthesis and the curve of the group of patients with dementia and partial prosthesis.

Table 1. Univariate statistical analysis of the baseline characteristics of patients with hip fracture differentiated by a previous diagnosis of dementia

		Total		Without dementia		With dementia		P value
		N	%	N	%	N	%	
Patients		5,867		4,204		1,663		
Follow-up (years)	Mean (SD)	3.92 (2.87)		4.29 (2.92)		2.98 (2.50)		0.000
Age (years)	Mean	82.70		81.91		84.71		0.000
	<80 years	1,618	27.6%	1,338	31.8%	280	16.8%	0.000
	≥80 years	4,249	72.4%	2,866	68.2%	1,383	83.2%	
Sex	Woman	4,340	74.0%	3,046	72.5%	1,294	77.8%	0.000
	Man	1,527	26.0%	1,158	27.5%	369	22.2%	
ASA risk	I-II	3,094	52.7%	2,281	54.3%	813	48.9%	0.000
	III-IV	2,773	47.3%	1,923	45.7%	850	51.1%	
Prosthesis	Total	1,307	22.3%	1,131	26.9%	176	10.6%	0.000
	Partial	4,560	77.7%	3,073	73.1%	1,487	89.4%	
Prosthesis-age group	Total, <80 years	798	13.6%	743	17.7%	55	3.3%	0.000
	Total, ≥80 years	509	8.7%	388	9.2%	121	7.3%	
	Partial, <80 years	820	14.0%	595	14.2%	225	13.5%	
	Partial, ≥80 years	3,740	63.7%	2,478	58.9%	1,262	75.9%	
Death	No	1,826	31.1%	1,534	36.5%	292	17.6%	0.000
	Yes	4,041	68.9%	2,670	63.5%	1,371	82.4%	
	<80 years	766	19.0%	555	20.8%	211	15.4%	0.000
	≥80 years	3,275	81.0%	2,115	79.2%	1,160	84.6%	

[a] Fisher's exact test was used for categorical variables and Student's t test for continuous variables; SD: standard deviation.

Table 4 shows the results of the two Cox regressions performed in the form of hazard ratios and significance. In the first Cox model, developed for all patients with hip fracture, age, sex, ASA risk, and group, according to dementia diagnosis and type of prosthesis, were found to be statistically significant. The risk was higher the older, in men and in patients with worse ASA. Regarding the group, the group of patients without dementia and full prosthesis was used as a reference and it was observed that the risk was 1.56 times higher for the group without dementia and partial prosthesis, 2.27 times higher for the group with dementia and total prosthesis and 2.37 times greater for the group with dementia and partial prosthesis. However, when performing the second Cox model only for patients with dementia, the ASA risk and the type of prosthesis were not statistically significant.

Discussion

Two findings stand out as the main results of our study. First, the previous diagnosis of dementia in patients who have suffered a hip fracture determines a great reduction in their life expectancy. Second, in patients with dementia, the type of prosthesis does not modify survival. These data are consistent with the clinical recommendations for the indication of a total hip arthroplasty as it is reserved for those patients with greater functional capacity, less comorbidity and high life expectancy[12].

Three treatment options for hip fractures are conservative without surgery, osteosynthesis of the fracture or different types of prostheses. In our series, only patients with displaced femoral neck fracture were included, those who are treated by arthroplasty, either partial or total, and in whose indication for a surgical procedure life expectancy plays a key role. Hip fractures without surgery were not included because the clinical interest of the survival analysis is due to the fact that it is a criterion for deciding the type of surgical procedure or the patients with fractures in the trochanteric area in whom the surgical management is different. Partial arthroplasty, preferably cemented, is the most indicated option for those patients with a limited life expectancy, with poorer function and mobility, or with cognitive alterations[13]. In recent years there has been an increase in the use of total arthroplasty for the surgical treatment of femoral neck fractures[13], but an analysis of results from the clinical and also the economic point of view is necessary to know in what type of patients its use is more efficient. Total arthroplasty is more expensive, requires a longer surgery time, is more aggressive for the patient and with a higher probability of postoperative anemia and the need for transfusions. In addition, we should bear in mind that patients with dementia have a higher risk of prosthetic dislocation and periprosthetic fracture[14]. In our sample, only 176 patients with dementia underwent total arthroplasty. Although it has been a small number, our results indicate that it is not the most appropriate option given that these pa-

Figure 1. Survival curves of patients with hip fracture differentiated by previous diagnosis of dementia

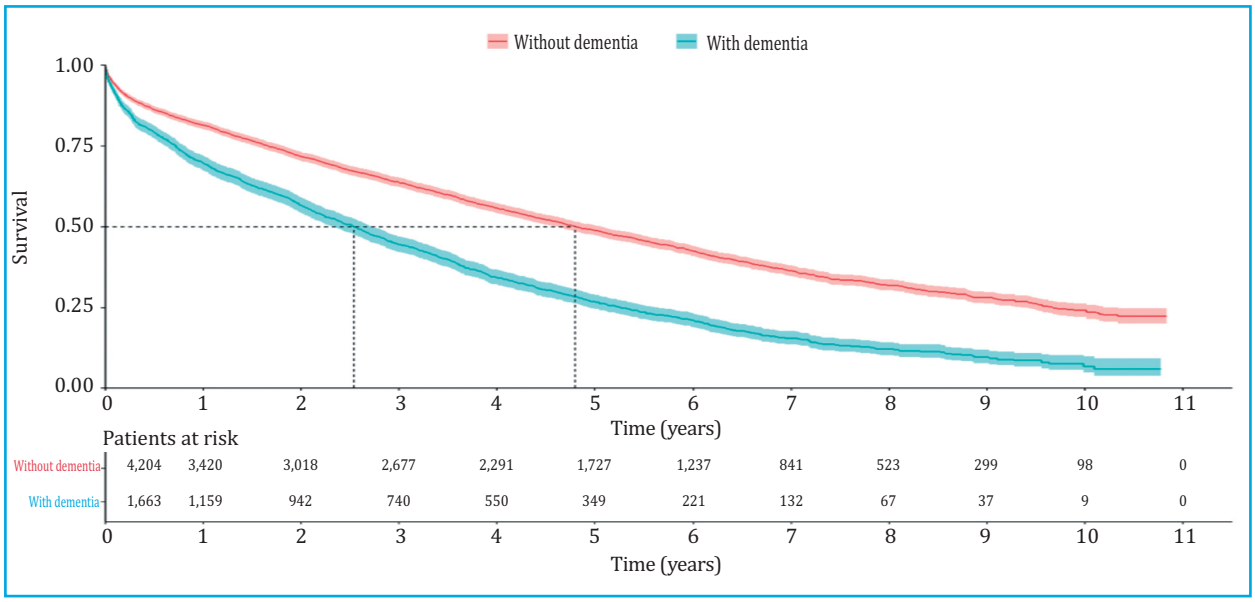
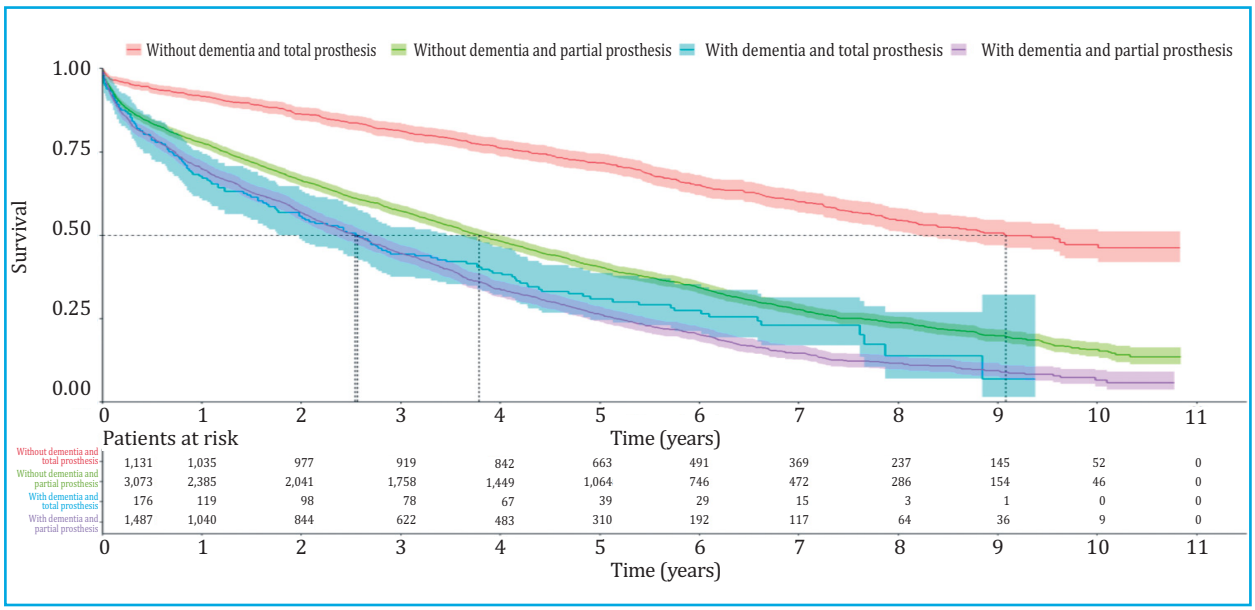


Figure 2. Survival curves of patients with hip fracture differentiated by previous diagnosis of dementia and type of prosthesis



tients' mortality is similar to that of patients who received a partial prosthesis. If the surgeon considers a total arthroplasty, the so-called double mobility prosthesis, should be indicated, the risk of dislocation is significantly reduced[15].

Hip fracture, in turn, can also be a risk factor for developing dementia. The main cause lies in the delirium that some of these patients experience during the postoperative period, which is estimated to increase the risk of developing dementia by up to 15 times in the 3 years after the fracture[16]. In addition, other factors have been related, such as the inflammatory response during the fracture consolidation process, the alteration of motor function and a decrease in physical activity after it, and the medication they receive during the process - before, during and after surgery- which could influence cognitive impairment[17].

Our results, referring to patients operated on with prostheses, are consistent with those described in the literature. A clear decrease in survival in patients with hip fracture in general were reportedly diagnosed with dementia. This is considered an independent risk factor for mortality after a hip fracture, since it behaves like the worst of the concomitant diseases[18], worsening functional recovery and vital prognosis. The reasons may be that these patients have more limitations in following postoperative instructions, more difficulties in exercising rehabilitation and a higher risk of malnutrition[19]. Mortality is also influenced by age, male sex, medical comorbidities (which may delay surgery), anesthetic risk, and functional status before the fracture. Dementia also increases the risk of suffering respiratory and urinary infections and more tendency to

Table 2. Follow-up indicating the 50% probability of survival for each group and differentiated by previous diagnosis of dementia and type of prosthesis according to the Kaplan-Meyer analysis

	Total	Without dementia	With dementia	Without dementia and total prosthesis	Without dementia and partial prosthetics	With dementia and total prosthesis	With dementia and partial prosthetics
Patients	5,867	4,204	1,663	1,131	3,073	176	1,487
50% chance	3.96	4.80	2.54	9.08	3.79	2.55	2.54

Table 3. Pairwise comparison of the survival curves of patients with hip fracture differentiated by previous diagnosis of dementia and type of prosthesis

	Without dementia and total prosthesis[a]	Without dementia and partial prosthetics [a]	With dementia and total prosthesis[a]	With dementia and partial prosthetics[a]
Without dementia and total prosthesis	-	0.00	0.00	0.00
Without dementia and partial prosthesis	0.00	-	0.00	0.00
With dementia and total prosthesis	0.00	0.00	-	0.19
With dementia and partial prosthesis	0.00	0.00	0.19	-

[a] Log rank test compared the survival curves of the four groups.

Table 4. Risk of death in all patients with hip fracture and in patients with hip fracture plus a diagnosis of dementia presented as hazard ratio and significance

All patients with hip fracture (N=5,867)	HR[a]
Age	1.06 (1.05-1.06) **
Gender: Male	1.86 (1.74-2.00) **
ASA risk: III- IV	1,28 (1.21-1.37) **
Dementia: No, Prosthesis: Total	Reference
Dementia: No, Prosthesis: Partial	1.56 (1.40-1.73) **
Dementia: Yes, Prosthesis: Total	2.27 (1.87-2.77) **
Dementia: Yes, Prosthesis: Partial	2.37 (2.11-2.66) **
Patients with hip fracture and diagnosis of dementia (N=1.663)	**HR[a]**
Age	1.05 (1.04-1.06) **
Sex: Man	1.85 (1.63-2.10) **
ASA risk: III- IV	1.07 (0.96-1.19)
Prosthesis: Partial	1.06 (0.88-1.27)

* P value ≤0.05; ** p value ≤0.01; [a] Calculated using Cox regression; HR = hazard ratio.

sepsis[20]. Some studies report an increase in mortality at one month[21,22], at 6 months[22,23], at one year[19,22] and with longer follow-ups[22] after the fracture. Ortho-geriatric functional recovery programs are beneficial in the acute phase, reducing mortality and institutionalization, although it is not clear which is the most appropriate approach[24].

Regarding these patients' treatment, the fact that on many occasions they present a high number of comorbidities and that the greater the clinical complexity, the worse the results[25], makes it possible to consider the surgery that is as less invasive as possible, for example with a simple osteosynthesis of the fracture or even, with surgical abstention. However, this extreme does not seem advisable since without surgery, mortality doubles at 6 months[26], along with increasing complications such as pressure ulcers and pain, which are very limiting and hinder simple care tasks such as hygiene or postural changes.

Our work has some limitations. As previously noted, we only include those patients operated on with a prosthesis, excluding patients with a fracture in the trochanteric region and also those patients who underwent osteosynthesis. However, the profile of the patient who undergoes a total prosthesis for a femur neck fracture is a more active patient with a theoretically longer life perspective, in which dementia plays a relevant role in its evolution. In the same way, we have been able to analyze the number of total arthroplasties in these types of patients, whose indication is debatable and indicates that clinical results such as survival should be measured in order to assess their use. Another limitation is that we do not assess the degree of

dementia or the number of falls that patients have, as well as the bone status or the diagnosis of osteoporosis or the antiosteoporotic medication that the patient may receive, although we recognize that they may influence their clinical development.

In conclusion, our study shows how dementia influences the survival curve of patients who underwent arthroplasty after a femoral neck fracture, and that patients with total arthroplasty present a similar mortality rate than patients who underwent partial prosthesis. Thus, we consider the indication of a more aggressive surgery in this type of patient should be avoided.

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Influence of breastfeeding on bone mineral metabolism after menopause

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Summary

Objective: Lifestyle and gynecological history appear to influence bone mineral metabolism. There are conflicting data on the possible effects of breastfeeding on the subsequent development of densitometric osteoporosis or the development of fragility fractures. The objective of this study was to assess these effects.

Material and methods: Observational, cross-sectional, open study, carried out in 758 postmenopausal women who were classified into two groups, depending on whether they had breastfed their children or not. Data were collected on lifestyles, gynecological history and fragility fractures. They underwent a general analysis, with renal and hepatic function, lipids, ions, as well as biochemical markers of bone remodeling, parathyroid hormone (PTH) and vitamin D (25HCC). Bone mineral density (BMD) was determined in the lumbar spine and in the proximal extremity of the femur by dual X-ray absorptiometry (DXA). Likewise, a quantitative ultrasound (QUS) measurement was performed on the calcaneus of the dominant foot. The raw data, after being compared by groups, were adjusted by applying the propensity score matching method, making a more precise comparison of the variables studied.

Results: The results prior to the application of the propensity score were adjusted for age and body mass index (BMI), since in the baseline study there were significant differences in these variables between both groups (prevalence of hip fractures and kyphosis and in the following biochemical parameters: specifically uric acid, glucose, HDL-cholesterol, triglycerides and phosphorus). These differences disappeared after adjusting for the variables that were included in the model by the applied linear logistic regression.

After adjusting with the propensity score matching and with the finally obtained linear regression model, no influence of breastfeeding was obtained on bone mineral density, on the prevalence of densitometric osteoporosis or on the appearance of fragility fractures after menopause.

Conclusion: Breastfeeding is not associated with higher or lower bone mineral density values, the prevalence of densitometric osteoporosis, or the presence of fragility fractures.

Key words: breastfeeding, pregnancy, osteoporosis, fragility fractures, propensity score matching, bone density.

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Introduction

Osteoporosis is defined as a skeletal disease in which there is a decrease in bone strength that leads to an increased risk of fracture, usually due to mild trauma[1]. Although any fracture can be observed in clinical practice, with the exception of the skull bones, the most prevalent is the vertebral one and the most serious that of the proximal extremity of the femur[2], given its significant morbidity and mortality[3]. Genetic, anthropometric, nutritional and lifestyle factors[4-11] influence the appearance of fragility fractures or osteoporotic fractures, but also gynecological and obstetric factors[12]. Among them, breastfeeding reportedly exerts an essential reproductive function in women and protects the mother from developing many diseases, such as cancer or diabetes[11-14].

Its effect on bone mineral metabolism is less defined, however, and published results are often contradictory. Some of these studies indicate that prolonged breastfeeding could be associated with an increase in bone mineral density (BMD) and a lower prevalence of osteoporosis in postmenopausal women[12-16], while others suggest precisely the opposite, that prolonged breastfeeding is a risk factor for the appearance of osteoporosis and fragility fractures[17-21]. Finally, reports have also been published that do not find any effect, neither beneficial nor harmful[22-24].

Therefore, we have carried out the present study in a population of postmenopausal women to establish whether or not breastfeeding is associated with the subsequent appearance of densitometric osteoporosis and the presence of fragility fractures, with the particularity that the propensity score matching method was used. This provides a more precise comparison of the variables studied in the established groups, making them more homogeneous as we will describe in more detail in this paper.

Material and methods

A total of 758 women were included, who were studied in the Bone Metabolic Unit of the Insular University Hospital in the period between 2016-2020. They were informed of the objectives of the study and gave their informed consent. All completed a questionnaire, previously validated and used in other similar clinical studies on osteoporosis[25,26]. They also underwent a basic physical examination that included height and weight measurements to then calculate their body mass index (BMI). Subsequently, they were grouped into women who had breastfed (cases) and women who did not (controls).

Sample collection and laboratory techniques

Blood and urine samples were collected in the morning, between 8:00 and 9:00 am, after an overnight fast. Blood was collected in the appropriate specific tubes for each determination, with the least possible venous compression, and was centrifuged at 1,500 g for 10 minutes; the serum was separated into aliquots and stored within one hour from the extraction at -20ºC until the biochemical analyzes were carried out, although most of them were carried out the same day as the extraction. Glucose, urea, creatinine, calcium, inorganic phosphorus, total proteins, total cholesterol and its fractions and triglycerides were measured using standardized and automated colorimetric techniques on an autoanalyzer (Kodak Ektachem Clinical Chemistry Slides).

Serum calcium was corrected according to total proteins by means of the following formula:

Corrected calcium = previous calcium (mg/dl)/
[0.55 + total proteins (g/l)/16]

Determination of ultrasound values in the calcaneus

Ultrasonographic parameters were estimated in the calcaneus of the dominant foot using a Sahara® Hologic® ultrasonographer (Bedford, Massachusetts, USA). This device measures both the broadband ultrasound attenuation (BUA) and the speed of sound (Speed of sound, SOS) in the region of interest of the calcaneus. The BUA and SOS values are combined into a single parameter called the quantitative ultrasound index (QUI), also known as the consistency or stiffness index, which is obtained by means of the formula:

QUI = 0.41 (SOS) + 0.41 (BUA) - 571

The T-score values were calculated from the values published as normal for the Spanish population[27].

Bone mineral density (BMD)

BMD was measured by dual radiological absorptiometry (DXA), both in the lumbar spine (L2-L4) and in the proximal extremity of the femur, with a Hologic Discovery® densitometer (Hologic Inc, Waltham, USA), whose accuracy is 0.75-0.16%. The measurements were made by the same operator, so there was no inter-observer variation. The T-score values were calculated from the values published as normal for the Canary Island population[28].

Diagnosis of osteoporosis and fragility fractures

Osteoporosis was considered to exist when a T-score equal to or less than -2.5 was obtained in any of the 3 anatomical locations where bone mineral density was determined: lumbar spine L2-L4, femoral neck or total hip.

The existence of a fragility fracture was diagnosed when they occurred without a trauma to justify it or when a maximum fall from the height of the woman in question. The fractures were confirmed by medical reports available in their medical history: emergency services, trauma, rehabilitation, or after analyzing x-rays.

Ethics

Our study was carried out in accordance with the standards of the Declaration of Helsinki[29] and was approved by the Ethics Committee of the Insular University Hospital. All patients were informed of the objectives of the study and their informed consent was requested.

Statistic analysis

Univariate analysis

Initially, we carried out an analysis of the numerical variables, studying whether or not they followed a normal distribution. Later we carried out a descriptive study. Categorical variables were summarized by percentages, and numerical variables by means and standard deviations if they followed normality, or as median and their interquartile range (percentiles = 25^{th} – 75^{th}) if they did not. To study the possible associations between categorical variables, the Chi-square test (χ^2) was used and the odds ratio (OR) was used as a measure of association, which was estimated using a 95% confidence interval (95% CI). In those cases in which there were cells with less than 5 cases, Fischer's exact test was applied.

Table 1. Baseline characteristics of the women studied

	Breastfeeding		
	Yes N = 457	**No N = 301**	**P value**
Age (years)	63.4 ± 11.7	57.3 ± 13.8	**<0.001**
BMI* (kg/m^2)	27.8 ± 5.1	26.4 ± 6.1	**<0.001**
Tobacco use, n (%)			0.787
Yes	71 (15.5)	52 (17.3)	
No	305 (66.7)	199 (66.1)	
Ex-smoker	81 (17.7)	50 (16.6)	
Alcohol use, n (%)			0.582
Yes	205 (45.0)	126 (41.9)	
No	246 (53.9)	173 (57.5)	
Ex-drinker	5 (1.1)	2 (0.7)	
Physical activity, n (%)			0.897
Sedentary	303 (67.2)	205 (68.8)	
Light	123 (27.3)	77 (25.8)	
Moderate	25 (5.5)	16 (5.4)	
Diabetes			0.696
Insulin-dependent	9 (2.0)	6 (2.0)	
No insulin-dependient	53 (11.6)	29 (9.6)	
No diabetes	395 (86.4)	266 (88.4)	
Fractures, n (%)			
All fractures	157 (34.4)	84 (28.1)	0.071
Vertebral	45 (10.3)	26 (9.3)	0.665
Hip	20 (4.6)	4 (1.4)	**0.023**
Colles	36 (8.2)	20 (7.1)	0.606
Falls	167 (37.0)	93 (31.0)	0.089
Kyphosis	114 (25.5)	48 (16.0)	**0.002**
Current calcium intake (mg/día)	700 (600-850)	700 (537-850)	0.425

The data are expressed as means ± standard deviations, medians (IQR) and frequencies in number (%); * BMI: body mass index.

To evaluate the association between a quantitative variable and a categorical variable, the Student's t-test or ANOVA (if there were more than 2 categories) was used for variables with normal distribution, or the non-parametric Mann-Whitney U test for the non-normal ones. In all cases, the significance level was considered at 5% ($p<0.05$).

Propensity score matching

To establish the association between breastfeeding and the presence of fragility fractures more precisely and to eliminate the influence of other variables, a similar non-lactating control (matching) was selected for each case of lactating women. This process was based on the method called propensity score matching, which in our case is defined by the conditional probability that breastfeeding is conditioned by those variables that could act as confounding factors. The propensity score was obtained for each patient using logistic regression, in which the final variable was breastfeeding. The co-variates included in the model were selected using the complete enumeration algorithm and the Akaike information criteria (Akaike Information Criterion, AIC).

Matching

Subsequently, we performed an adjusted 1 to 1 analysis without replacement, based on the propensity score of each patient. The caliper or calibrator chosen was 0.7. After adjustment for the propensity score, the baseline characteristics were compared by McNemar's test for binary variables or with the t-test or Wilcoxon, as appropriate in each case, for continuous variables and paired data. The 13 variables selected by the program to be included in the matching were: age, BMI, falls, use of statins or thiazides, uric acid, total cholesterol, HDL-cholesterol, triglycerides, the presence of kyphosis and densitometric

Table 2. Bone mineral density values obtained by densitometry (DXA) and ultrasound (QUS), values adjusted for age and BMI and prevalence of densitometric osteoporosis

	Yes N = 457	No N = 301	P value
Densitometry (DXA)			
L2-L4 (g/cm^2)	0.828 (0.7 ; 0.942)	0.842 (0.7 ; 0.980)	0.624
T-score	-2.0 (-2.8 ; -0.942)	1.9 (-3.0 ; -0.5)	
Femoral neck (g/cm^2)	0.655 (0.6 ; 0.738)	0.673 (0.6 ; 0.768)	0.080
T-score	-1.6 (-2.3 ; -0.9)	-1.5 (-2.3 ; -0.6)	
Total hip (g/cm^2)	0.784 (0.7 ; 0.881)	0.788 (0.7 ; 0.893)	0.923
T-score	-1.2 (-1.3 ; -1.1)	-1.2 (-1.3; -1.0)	
Ultrasounds(QUS)			
BUA (dB/mHz)	60.8 (58.9 ; 62.7)	60.9 (58.6 ; 63.2)	0.950
SOS (m/s)	1522 (1519 ; 1525)	1522 (1518 ; 1526)	0.963
QUI	78.1 (76.0 ; 80.1)	77.7 (75.2 ; 80.2)	0.824
Densitometric osteoporosis*, n (%)	205 (44.9%)	134 (44.5%)	0.927

Median (95% CI) adjusted for age and body mass index (BMI); *: presence of a T-score lower than -2.5 in any of the 3 locations where bone mineral density (DXA) was determined, expressed in number (%).

values in L2-L4, femoral neck and total hip. Furthermore, we established the success of the propensity score adjustment by balancing the adjustment of the covariates in the two groups using the standardized differences. Those differences less than 10% supported the assumption of equilibrium between the two groups. The level of statistical significance was established at 5% ($p<0.05$). The data were analyzed using the R program, version 3.6.1 (R Development Core Team, 2019).

Results

Table 1 of the women included in the study, grouped into women who had breastfed and women who had not. Those who had breastfed were older (63.4 ± 11.7 years versus 57.3 ± 13.8 years, $p<0.001$) and had a higher BMI, (27.8 ± 5.1 kg/m^2 versus 26.4 ± 6.1 kg/m^2), were performed after adjusting for these two variables. The prevalence of hip fracture was higher among women who had breastfed significantly, a significance that subsequently disappeared when adjusting for age and BMI.

Table 2 shows the BMD values obtained in the lumbar spine (L2-L4) and in the proximal extremity of the femur with their corresponding T-scores. The ultrasound index values obtained in the calcaneus are also shown, specifically the ultrasound attenuation coefficient (BUA), the speed of sound (SOS) and the consistency index or stiffness (QUI). No statistically significant differences were observed in any of the values obtained between both groups studied. The prevalence of osteoporosis was similar between both groups: 44.9% in women who had breastfed and 44.5% in those who had not, ($p=0.927$).

Table 3 shows the biochemical values obtained in both groups studied before making the adjustment. Statistically significant differences ($p<0.05$) are observed in the serum values of uric acid, HDL-cholesterol, triglycerides and phosphorus. All of these differences subsequently disappeared when propensity score matching was carried out.

Table 4 sets out the characteristics of the study patients after matching according to the propensity score of each of them. The variables selected by the program to carry out said matching are shown, which were a total of 13, including all those that had previously shown statistically significant differences in the crude comparisons. As a consequence of this matching, the sample size was substantially reduced to the point that the number of women was finally made up of 254 women in each group. As proof of the correctness of this pairing, it is observed that the standardized differences are less than 10%, which indicates the homogeneity of the variables between both groups.

Table 5 shows the data obtained by applying conditional logistic regression for the presence of fragility fractures. After matching, breastfeeding showed no association with fragility fractures.

Discussion

Osteoporosis is a very prevalent disease in which fractures are its only clinical complication[2,30]. Various risk factors have been implicated in the etiopathogenesis of postmenopausal osteoporosis, related to lifestyle[4-7,12], genetics[8] and even gynecological history[12,14].

One of the etiopathogenic aspects on which there is no consensus is the effect that breastfeeding, which is carried out at a stage of life in which the woman is obviously younger, may have on the subsequent development of osteoporosis after menopause. Some studies suggest that the “negative calcium balance” that would occur during breastfeeding could generate a subsequent loss of bone mass that would manifest itself after menopause with an increased risk of developing densitometric osteoporosis and/or fragility fractures[17-21].

Table 3. Biochemical data of the patients included in the study, classified according to whether they had breastfed or not, adjusted for age and BMI

	Breastfeeding		
	Yes N = 457	No N = 301	P value
Urea (mg/dL)	34 (28 - 41)	33 (27 - 40)	0.189
Creatinine (mg/dL)	0.8 (0.8 - 0.9)	0.8 (0.8 - 0.9)	0.460
Uric acid (mg/dL)	4.3 (3.7 - 5.2)	4.2 (3.6 - 5)	**0.028**
Glucose (mg/dL)	96 (89 - 105)	95 (88 - 103)	**0.054**
Total cholesterol (mg/dL)	213 (186 - 238)	212 (186 - 240)	0.843
HDL-cholesterol (mg/dL)	59 (50 - 68)	61 (51 - 72)	**0.040**
LDL-cholesterol (mg/dL)	128 (106 - 151)	130 (108 - 158)	0.615
Triglycerides (mg/dL)	110 (82 - 150)	98 (75 - 126)	**<0.001**
Calcium (mg/dL)	9.9 (9.5 - 10.3)	9.8 (9.4 - 10.2)	0.092
phosphorus (mg/dL)	3.4 (3.1 - 3.8)	3.5 (3.1 - 3.9)	**0.029**
Total proteins (g/L)	7.1 (6.9 - 7.5)	7.1 (6.9 - 7.4)	0.924
25-hydroxycholecalciferol (ng/mL)	22.1 (16 - 30)	21.9 (16 – 31.1)	0.565
Parathyroid hormone (PTH) (pg/mL)	48 (36 - 75)	46 (35 - 70)	0.609
FATR* (UI/L)	82 (63 - 104)	79 (65 - 98)	0.694
Beta-crosslaps (ng/mL)	0.4 (0.2 - 0.61)	0.4 (0.2 - 0.61)	0.807
Osteocalcin (ng/mL)	20 (13 - 31)	19 (12 - 29)	0.319
Type I procollagen (P1NP) (ng/mL)	43 (31 - 60)	43 (27 - 59)	0.412

* FATR: tartrate-resistant acid phosphatase.

In fact, during lactation, the mother supplies the fetus with around 300 mg of calcium daily, the source of which is mainly bone, which produces a loss of between 5-10% of maternal bone mass[31], being enough for 3-6 months lactation for this loss to occur[32]. However, when studying and trying to establish the gynecological and/or obstetric factors that can influence bone mineral metabolism, some authors assess only the presence or absence of pregnancies[16], others study the number of pregnancies[21] with no shortage of who analyzes the age at which the first pregnancy occurs[20]. On the other hand, other authors suggest that the organism adapts to this situation, since it is transitory. With several compensatory homeostatic mechanisms, it restores balance in bone mineral metabolism. Other authors suggest that when breastfeeding lasts up to one year, it would be correct to inform the mother of the need for her to acquire nutritional and physical activity habits that facilitate this recovery[33,34].

There are also notable differences in the method to be used to assess the effect of breastfeeding on bone mineral metabolism. Some studies analyze changes in BMD[16,35], while others consider the risk of developing fragility fractures[12,15,36], especially hip fractures[18,37]. Interestingly, we have not found studies in the literature that analyze the effect of breastfeeding on a very significant aspect of the skeleton, which is bone quality, to such an important extent that some authors consider that it contributes more to fracture risk than the amount measured by BMD[38].

Some studies have been carried out in order to know what are the changes in bone mineral metabolism in women at the time they are breastfeeding. Thus, Carneiro et al. suggested the hypothesis that in these women there is an uncoupling between osteoblasts and osteoclasts that leads to a rapid loss of bone mass[39].

In a review carried out by Sower on the effect of pregnancy and lactation on bone mineral metabolism, a wide variability is collected in the results obtained in the different publications, which is considered to be largely due to the heterogeneity of the methodology used in these studies[40].

A total of 758 women were included in our study, of whom 301 (39.7%) had not breastfed and 457 (60.3%) had. All of them were postmenopausal and in the analysis of their clinical characteristics in the baseline evaluation, we found the existence of statistically significant differences in age and BMI, which is why the densitometric values and the analytical parameters collected in Tables 2 and 3 are compared after adjusting for these two variables.

Table 4. Characteristics of the study women after propensity-score matching

	Breastfeeding			
	Yes N = 254	**No N = 254**	**p value**	**% of standardized difference***
Age (years)	60.4 ± 11.0	60.1 ± 11.1	0.712	-2.9676
BMI (kg/m^2)	27.2 ± 5.7	27.0 ± 6.2	0.665	-3.4992
Falls	80 (31.5)	82 (32.3)	0.923	1.6807
Statins	79 (31.1)	86 (33.9)	0.550	5.8122
Thiazides	26 (10.2)	23 (9.1)	0.775	-4.1077
Uric acid (mg/dL)	4.4 ± 1.2	4.4 ± 1.3	0.567	-4.8984
Total cholesterol (mg/dL)	214.7 ± 39.1	216.7 ± 45.9	0.615	4.2572
HDL-cholesterol (mg/dL)	62.4 ± 15.0	62.1 ± 16.1	0.845	-1.6184
Triglycerides (mg/dL)	4.6 ± 0.4	4.6 ± 0.4	0.711	2.8626
L2-L4 (g/cm^2)	0.8 ± 0.2	0.8 ± 0.2	0.972	0.2958
T-score	-1.9 ± 1.5	-1.8 ± 1.7		
Femoral neck (g/cm^2)	0.7 ± 0.1	0.7 ± 0.1	0.258	9.1552
T-score	1.5 ± 1.1	-1.4 ± 1.2		
Total hip (g/cm^2)	0.8 ± 0.1	0.8 ± 0.2	0.880	1.2448
T-score	-1.3 ± 1,4	-1.2 ± 1.6		
Kyphosis	53 (20.9)	46 (18.1)	0.470	-7.1422
Fragility fractures n (%)	75 (29.5)	74 (29.1)	1	-0.8647
Densitometric osteoporosis** n (%)	115 (44.1)	117 (44.8)	0.933	-1.540

Data are expressed as mean ± standard deviation and frequencies: n (%); the calibrator (caliper) selected was 0.5; *: note that all standardized differences were less than or equal to 10%; **: presence of a T-score lower than -2.5 in any of the 3 locations where bone mineral density (DXA) was determined.

Table 5. Conditional logistic regression for the presence of fragility fractures. After matching, breastfeeding showed no association with fragility fractures

	Breastfeeding		p value*	OR (95% CI)**
	Yes N = 254	**No N = 254**		
Fragility fractures			0.002	-
No, n (%)	179 (70.5)	180 (70.9)		1 (Reference)
Yes, n (%)	75 (29.5)	74 (29.1)		1.018 (0.704 – 1.447)

*: likelihood ratio test; **: conditional logistic regression; OR: odds ratio.

The distribution of lifestyles, such as tobacco use, physical activity in leisure time and the prevalence of diabetes, showed similar prevalence figures, without obtaining statistically significant differences. In a study by Yan et al. in Chinese women, they found that the differences observed in BMD in postmenopausal women who had breastfed and those who had not, were due to age, BMI and the number of pregnancies and not to the fact of having or not breastfed[21]. Given the known effect of age and BMI on BMD[9] in our study, we decided to adjust for these variables.

Women in both groups, lactating and non-lactating, showed similar BMD values in both the lumbar spine and the proximal end of the femur. Some studies have described that women who breastfeed have lower BMD values than those who do not[20,24,32], but there are other authors who find the opposite: a protective effect with higher BMD values and a lower risk of densitometric osteoporosis[18,31]. A study carried out in Korea in more than one million women[41] found that the parameters that were independently associated with an increased risk of

fracture were the presence of late menarche, early menopause and, therefore, a shorter reproductive period, but not breastfeeding, a finding that concurs with our results.

In the literature consulted, we did not find studies that linked breastfeeding with bone quality assessed by ultrasound in postmenopausal women, and we only found one study carried out in premenopausal women that reported a beneficial effect[42].

In our study, no statistically significant differences were observed in the ultrasound indices, so we can accept that breastfeeding has no effect, either positive or negative, on bone quality estimated by these measurements. We consider the statistically significant differences that we have found in the biochemical data to be clinically irrelevant[43], as they are within the range of normality established by the laboratory and do not have a clinical impact.

By applying the statistical technique of the propensity score matching method, we achieved a better fit of the women to homogenize both groups. The variables established by the program to be included in the adjustment are shown in table 4 and it can be seen that the standardized difference percentage ranges between -7.1422 and 9.1552. This indicates a very good fit, which has been established by consensus as less than 10%. Although as a consequence of this adjustment, the number of women studied decreased to 254 in each group, thanks to it we were able to establish more precisely, by applying conditional logistic regression, that breastfeeding has no effect on the presence of fragility fractures after menopause.

In conclusion, our study suggests that breastfeeding has no positive or negative effect on bone mineral metabolism after menopause, according to the biochemical results obtained (with markers of bone remodeling, vitamin D and PTH) and the densitometric (with DXA and QUS). Finally, the propensity score matching method allowed us to confirm that it did not influence the prevalence of fragility fractures after menopause either.

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

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Effect of vitamin D supplementation on aromatase inhibitor-related musculoskeletal side effects for breast cancer: B-ABLE cohort

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Summary

Objetive: To assess the effect of vitamin D supplementation on musculoskeletal complications related to aromatase inhibitor (AI) treatment in patients with breast cancer.

Material and methods: Prospective observational study of women undergoing AI treatment, recruited in the B-ABLE cohort. Patients with baseline serum 25 (OH) D (25-hydroxyvitamin D) levels <30 ng/ml received a 16,000 IU dose of oral calcifediol every 2 weeks. Arthralgia and bone loss related to AIs were assessed at 3 months and 1 year of follow-up, respectively. The association analyzes of vitamin D status at 3 months with musculoskeletal events were carried out using adjusted multivariate linear regression models. In addition, the association of incident pain, defined as patients without initial joint pain, but with a visual analog scale (VAS) >0 at 3 months, was evaluated using logistic regression.

Results: Vitamin D supplementation at the start of AI treatment decreased the risk of both incident arthralgia and its worsening. The effective threshold of 25 (OH) D in serum to reduce joint pain was established at 40 ng/ml. However, this threshold was not significantly related to bone changes at one year of follow-up. However, vitamin D levels were inversely correlated with lumbar spine bone loss (LS) (β=0.177% [95% CI: 0.014 to 0.340]).

Conclusions: Vitamin D supplementation aimed at achieving serum 25(OH)D levels of at least 40 ng/ml is protective for arthralgia. Vitamin D levels at three months could predict the risk of bone loss in LS at one year of AI treatment. Therefore, high doses of vitamin D are recommended in these patients, who are more prone to musculoskeletal conditions.

Key words: aromatase inhibitors, vitamin D, breast cancer, bone loss, arthralgia.

Introduction

Survival for patients who suffer estrogen receptor positive (ER+) breast cancer has improved dramatically over the years due to the addition of adjuvant hormonal therapy, especially aromatase inhibitors (AI). Letrozole, anastrozole and exemestane are third generation AIs that massively reduce circulating estrogens in postmenopausal women. Although this effect is decisive for survival and the reduction of tumor relapse, it also leads to adverse events and quality of life problems, more prominently associated with the musculoskeletal system[1].

Its use in women as adjunctive treatment for 2-5 years has been correlated with an increased risk of bone loss and fractures[2,3]. Furthermore, AI administration is associated with the appearance and/or increase of arthralgia –described as joint pain– with an estimated incidence of 55% in a previous study by our group[4]. The high rate of arthralgias is of particular concern, since it is reportedly the most frequent reason for interrupting treatment[5,6]. Although practical guidelines have been developed to prevent and manage IA-related bone loss[7], effective treatment of arthralgia has yet to be addressed[8].

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Previous studies in the B-ABLE cohort, a clinical, prospective, cohort study of women diagnosed with early ER+ breast cancer, and candidates for aromatase inhibitor therapy, showed that low levels of 25-hydroxyvitamin D (25(OH)D) were associated with greater bone mass loss and worsening joint pain[9-11]. Similarly, IA-related arthralgia in the B-ABLE cohort was significantly reduced in those patients who achieved serum 25(OH)D concentrations ≥40 ng/ml[11]. Consequently, maintaining optimal 25(OH)D levels in the general population is strongly recommended to prevent not only bone loss but other non-skeletal disorders as well[12]. Therefore, assessment of serum 25(OH)D levels in breast cancer patients treated with AI could be important in preventing musculoskeletal disorders, as well as other issues that affect quality of life.

To further explore the association of vitamin D status with bone loss and arthralgia, the expanded B-ABLE cohort, comprised of 927 postmenopausal women diagnosed with RE+ breast cancer and treated with IA, was evaluated. This was intended to establish target 25 (OH) D threshold levels to prevent the appearance of arthralgias associated with AI.

Material and methods

Study design and participants

From January 2006 to January 2019, data were collected from 927 Caucasian postmenopausal women who had been diagnosed with ER+ early breast cancer and who were candidates for AI treatment (letrozole, exemestane, or anastrozole). These women were recruited into the B-ABLE cohort –an unselected, prospective clinical cohort study– at Hospital del Mar (Barcelona, Spain) (ClinicalTrials.gov 2019 Identifier: NCT03811509).

Participants were recruited 6 weeks after surgery or 1 month after the last chemotherapy cycle or, alternatively, once menopause began after taking tamoxifen (TAM) for 2 to 3 years. Postmenopausal status was defined as patients aged >55 years with amenorrhea of >12 months, or those aged ≤55 years with luteinizing hormone levels >30 mIU/ml and/or follicle-stimulating hormone levels >40 mIU/ml. Exclusion criteria were: previous history of any metabolic bone disorder, alcoholism, rheumatoid arthritis, and concurrent or previous treatment with oral corticosteroids. Patients with vitamin D levels ≥30 ng/ml were also excluded, as they did not receive vitamin D supplements.

At the outset of the study, all patients' bone mineral density (BMD) was evaluated in the lumbar spine (L1-L4), the femoral neck (FN) and the total hip (TH). Those with a T-score <-2.5 at any site, or with a T-score ≤-2.0 at any site plus a major risk factor[13], and/or previous fragility fractures, were treated with antiresorptive drugs, including weekly oral risedronate or alendronate, or denosumab every 6 months.

All participants with baseline serum levels of 25 (OH) D <30 ng/ml received a dose of 16,000 IU of oral calcifediol (Hidroferol® Faes Farma) every 2 weeks from the start of the study, in addition to calcium tablets and 25 (OH) vitamin D3 (1,000 mg and 800 IU daily, respectively) if your dietary calcium intake was less than 1,200 mg/day.

Variables

Visual analog scale

A visual analog scale (VAS) was used to record the intensity of self-reported joint pain at baseline (before starting AI treatment) and after 3 months of AI treatment. The score ranged from 0 (no pain) to 10 (maximum pain). The question associated with the VAS was the following "please indicate the intensity of the pain you feel in your peripheral joints (knee, wrist, fingers/toes, elbow, shoulder, etc.), excluding the spine/back pain and pain in the operated area"[11].

The administration of analgesics and anti-inflammatories was recorded and taken into account for the evaluation of pain.

Vitamin D levels

Vitamin D (25 (OH) D) levels were assessed at baseline and at 3-month follow-up in each study participant. Serum 25 (OH) D levels were obtained from peripheral blood using a competitive direct immunoluminometric assay with direct coated magnetic microparticles (coefficient of variation: <10%) (Elecsys Vitamin D total II, model 07028148190; Cobas e801 system, Roche Diagnostics GmbH, Mannheim, Germany).

Bone mineral density (BMD)

BMD measurements were made in the lumbar spine (LS), the neck of the femur (FN) and the total hip (TH) at the beginning and at 12 months of treatment with AI. BMD was measured with a DXA QDR 4500 SL® densitometer (Hologic, Waltham, Massachusetts, USA), according to the manufacturer's recommendations. In our unit, the in vivo coefficient of variation of this technique is 1.0% in LS, 1.60% in CT and 1.65% in CF.

Other variables

At the time of recruitment, data on clinical variables were recorded, such as: age, body mass index (BMI), age at menarche and menopause, number of children, total months of breastfeeding, spine x-ray and recent chemotherapy (women exposed to chemotherapy one month before recruitment), among others.

Statistical analysis

Descriptive data were presented using the mean or median depending on the nature of the variables. Differences between values at baseline and at 3 or 12 months were analyzed using the Wilcoxon paired samples test and the paired t test. Based on previous findings[11], four vitamin D thresholds were defined according to the patients' vitamin D concentrations at three months of follow-up: ≥20 ng/ml, ≥30 ng/ml, ≥40 ng/ml and ≥50 ng/ml. ml. The association between absolute changes in VAS from baseline to 3 months and vitamin D thresholds was analyzed using a multivariate linear regression model. Furthermore, the association of incident pain, defined as patients without initial joint pain, but with a VAS >0 at 3 months, and vitamin D thresholds, was evaluated using logistic regression. Regression analyzes were adjusted for age, BMI, recent chemotherapy, previous use of tamoxifen, and current use of bone antiresorptives. The linearity, interaction and absence of multicollinearity of the independent variables were checked.

Finally, a subset of participants not exposed to antiresorptive treatments was selected to assess the association between relative changes in BMD at 12 months and vitamin D thresholds, or vitamin D levels at 3 months, using linear regression. adjusting for age, BMI, years since menopause, recent chemotherapy, and prior tamoxifen use. In addition, the linearity of the independent variables was verified.

Statistical analyzes were carried out using R for Windows version 3.3.3, using foreign, compareGroups, car, QuantPsyc and gam. All statistical tests with $p<0.05$ were considered significant.

Ethics approval

The study protocol followed the standards of the Declaration of Helsinki and was approved by the Parc de Salut Mar ethics committee (2016/6803/I). Written informed consent was obtained from each participant once they had read the study information sheet and all their doubts were clarified. The privacy rights of human subjects were always respected.

Results

Participants

A total of 741 of the 927 patients recruited in the B-ABLE cohort were visited at the 3-month follow-up, had data available and had baseline serum 25 (OH) D levels below 30 ng/ml (Figure 1). and, therefore, they were eligible for the present study. The baseline characteristics of the selected patients are indicated in table 1.

AI-related arthralgia and vitamin D status at 3 months

At 3 months, the median [Q1;Q3] of the VAS increased from 2.00 [0.00;4.00] to 3.00 [0.00;5.00] ($p<0.001$), and the vitamin D increased from 15.10 [10.8;21.00] to 40.20 [30.90;52.50] ($p<0.001$). The change in VAS from baseline to 3 months was significantly associated with a vitamin D threshold ≥40 ng/ml ($p<0.05$) at 3 months of follow-up (Table 2), that is, an increase in VAS decreased 0.40 units in patients who reached a vitamin D threshold greater than 40 ng/ml with supplementation (Figure 2).

Incident pain was assessed in a subset of 301 patients without initial pain. Of these, 117 (38.87%) developed joint pain at 3 months with a median VAS [Q1;Q3] of 3.50 [2.20;5.00]. The logistic regression between vitamin D thresholds and the appearance of joint pain at 3 months showed that those patients who achieved vitamin D levels ≥40 ng/ml were less likely to experience incident pain ($p<0.05$) (Table 3 and Figure 3).

BMD and vitamin D status

Data from 473 patients who were not exposed to any antiresorptive treatment and who had BMD data at 12 months of follow-up were analyzed. In these patients, the BMD of the LS, FN and TH decreased significantly after 12 months of treatment with AI ($p<0.001$) (Table 4).

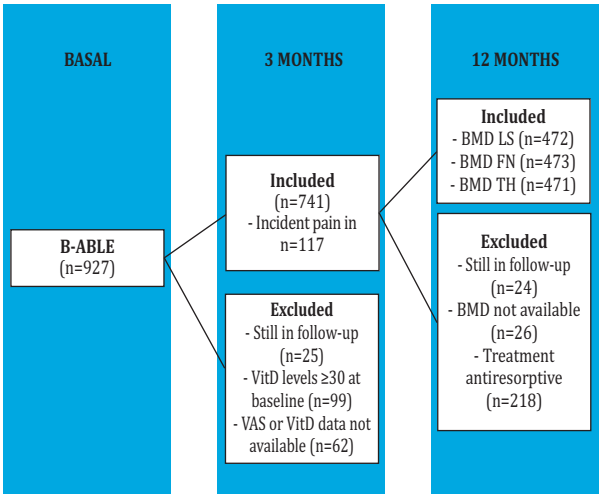
No association was detected between any of the vitamin D thresholds analyzed (≥20 ng/ml, ≥30 ng/ml, ≥40 ng/ml, or ≥50 ng/ml) at 3 months and the relative changes in BMD of LS, FN and TH at 12 months. However, each 10 ng/ml increase in serum vitamin D at three months was associated with a lower loss of BMD in LS (unadjusted $\beta = +0.194\%$ [95% CI: 0.028 to 0.359] and adjusted $\beta = +0.177\%$ [95% CI: 0.014 to 0.340]; $p<0.05$). No significant associations were observed between vitamin D levels and BMD of FN and TH.

Discussion

An observational, prospective, and real-life study of postmenopausal women treated with aromatase inhibitors included in the B-ABLE cohort was carried out. AI treatment in ER+ early breast cancer patients is strongly associated with musculoskeletal side effects. However, vitamin D supplementation early in AI appears to attenuate one of the main risk factors for treatment interruption: AI-related arthralgia. Our results suggest that AI-induced joint pain is vitamin D dependent, and that 40 ng/ml is the effective target threshold for serum 25 (OH) D levels to reduce the risk of both joint pain incidence and its worsening. However, this threshold is not significantly related to changes in BMD at one year of follow-up. However, vitamin D supplementation was inversely correlated with bone loss of CL, as each 10 ng/ml increase in serum 25 (OH) D at 3 months resulted in a reduction in blood pressure and 0.177% bone loss.

Vitamin D is known to play an important role in musculoskeletal tissues in addition to bone[14], including muscle[15], cartilage[16], and synovium[17]. Previous studies carried out in women with ER+ early breast cancer receiving AI treatment, who also frequently present vitamin D deficiency[18], provide evidence of the possible effects of vitamin D status on musculoskeletal health[9,19]. In our cohort study, the main musculoskeletal effect of vitamin D supplementation was found in AI-related arthralgia, consistent with a previous study by Prieto-Alhambra et al. in 2011[11]. Similarly, another observatio-

Figure 1. Flow chart showing the number of patient records included in each study point



BMD: bone mineral density; FN: femoral neck; LS: lumbar spine; TH: total hip; VitD: serum levels of 25-hydroxyvitamin D.

Table 1. Baseline characteristics of the patients

Variables	N=741
Age, years (Mean ± SD)	61.9 ± 7.89
BMI, kg/m² (Mean ± SD)	29.1 (5.36)
VAS (Median [Q1;Q3])	2.00 [0.00; 4.00]
Vitamin D, ng/ml (Median ± SD)	15.1 [10.8; 21.0]
BP, n (%)	149 (20.1%)
TAM, n (%)	223 (30.1%)
Recent CT, n (%)	279 (37.7%)

BMI: body mass index; BP: bisphosphonates; VAS: visual analog scale; TAM: tamoxifen; Q: quartile; CT: chemotherapy.

Table 2. Linear regression between the change in the VAS from baseline to 3 months and the vitamin D threshold at 3 months (in all patients n=741)

Threshold at 3 months	N (%) patients at threshold	Unadjusted β [IC 95%]	Adjusted β [IC 95%]
≥20 ng/ml	705 (95.01%)	0.03 [-0.78; 0.85]	0.19 [-0.63; 1.02]
≥30 ng/ml	567 (76.42%)	-0.05 [-0.47; 0.36]	-0.06 [-0.48; 0.36]
≥40 ng/ml	383 (51.62%)	**-0.39 [-0.74; -0.03]**	**-0.39 [-0.75; -0.04]**
≥50 ng/ml	225 (30.32%)	0.09 [-0.30; 0.47]	0.08 [-0.31; 0.46]

β: β-coefficient adjusted for age, BMI, recent chemotherapy, antiresorptive drugs and previous tamoxifen; CI: confidence interval. In bold: significant results (p<0.05).

Table 3. Logistic regression between incident pain and vitamin D threshold at 3 months (patients without initial pain n=301; of these, n=117 developed incident pain)

Threshold at 3 months	N (%) patients at threshold	Unadjusted OR [IC 95%]	Adjusted OR [IC 95%]
≥20 ng/ml	292 (97.00%)	0.79 [0.21; 3.00]	0.83 [0.21; 3.27]
≥30 ng/ml	242 (80.40%)	0.76 [0.43; 1.36]	0.81 [0.45; 1.46]
≥40 ng/ml	165 (54.82%)	**0.53 [0.33; 0.85]**	**0.55 [0.34; 0.90]**
≥50 ng/ml	106 (35.22%)	0.77 [0.47; 1.26]	0.81 [0.49; 1.34]

CI: confidence interval; OR: odds ratio, adjusted for: age, BMI, recent chemotherapy, antiresorptive drugs, and previous tamoxifen. In bold: significant results (p<0.05).

nal study showed that a high dose of vitamin D (50,000 IU weekly of vitamin D3 orally) improved arthralgia values in patients who achieved mean concentrations of 25 (OH) D higher than the mean of 66 ng/ml[20]. In our case, the threshold was defined as ≥40 ng/ml, which was reached after 3 months of vitamin D supplementation in approximately 50% of patients. Clinically, the fact of containing the increase in pain related to AI at 3 months helps to improve the patients' quality of life, as well as avoiding treatment discontinuity[21].

Unlike pain, changes in BMD usually take longer to notice. Bone remodeling is a progressive process that results in long-term changes in BMD. Therapeutic interventions on BMD are evaluated annually in routine clinical practice. For this reason, in our study, BMD was assessed after 1 year of follow-up. Associations with vitamin D intake were only detected in the lumbar spine, which is not surprising given that bone remodeling is more active in this area and the pharmacological effects are more visible in trabecular bone compared to other skeletal locations with greater cortical content. We observed that increases in serum 25 (OH) D at 3 months were inversely correlated with AI-related bone loss at 1 year, therefore, this increase in 25 (OH) D could predict bone behavior at 1 year, but only visible in column. This coincides with a previous study by Prieto-Alhambra et al.[22], although they found greater reductions in bone loss of 1.70%, in patients who achieved serum vitamin D levels ≥40 ng/ml.

This study has several limitations. First, this is not a randomized control trial, so the efficacy of high-dose vitamin D supplementation compared to a placebo group could not be assessed. Furthermore, compliance with vitamin D supplementation was not strictly controlled. This could explain the variability of 25 (OH) D levels between patients after 3 months of treatment. Finally, the current assumption that circulating 25(OH)D concentrations are a measure of vitamin D functional status may be incorrect. However, measuring 25(OH)D levels is the easiest and most reliable assessment of vitamin D status currently available.

Vitamin D supplementation administered to patients in specified doses increases levels from 15.10 [10.8;21.00] to 40.20 [30.90;52.50], thus reaching adequate levels of vitamin D at 3 months in most of the patients. The goal of therapy is to treat vitamin D insufficiency/deficiency rather than increase to supranormal concentrations, so we believe the risk of harm from administered doses is very low.

Our results suggest that optimal levels of vitamin D are associated with a reduced risk of joint pain related to AI treatment. A target threshold of 25OHD serum levels was set at 40 ng/ml to significantly reduce the increase in joint pain. It should be noted that this threshold is well above the goal of 20 ng/ml recommended by the 2010 Institute of Medicine (IOM) report[23]. Therefore, vitamin D supplements at the specified doses could be protective against arthralgia and AI-induced spinal bone loss. As a final observation, vitamin D supplements are inexpensive, safe, and easily accessible, making these drugs easy to use on a wide scale.

Figure 2. VAS changes are stratified by the vitamin D threshold of 40 ng/ml at 3 months, in all patients with baseline vitamin D levels ≤30 ng/ml. VAS values are reported as median [95% CI]

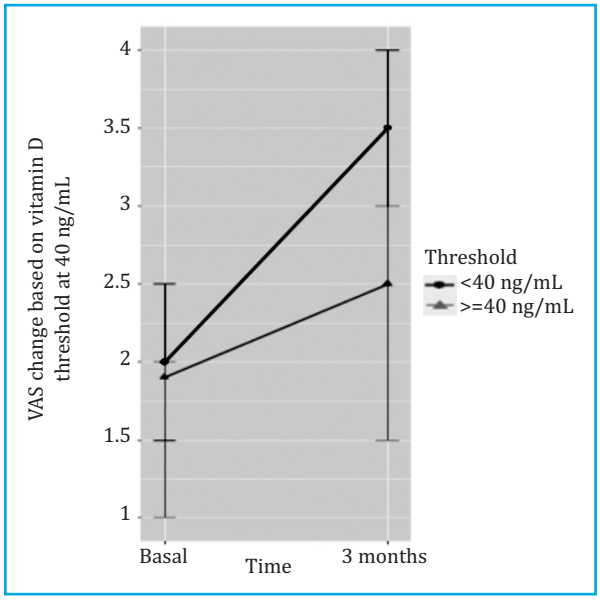


Figure 3. Changes in VAS in women with incident pain (n=117) and according to the vitamin D threshold of 40 ng/mL. VAS values are reported as median [95 CI)

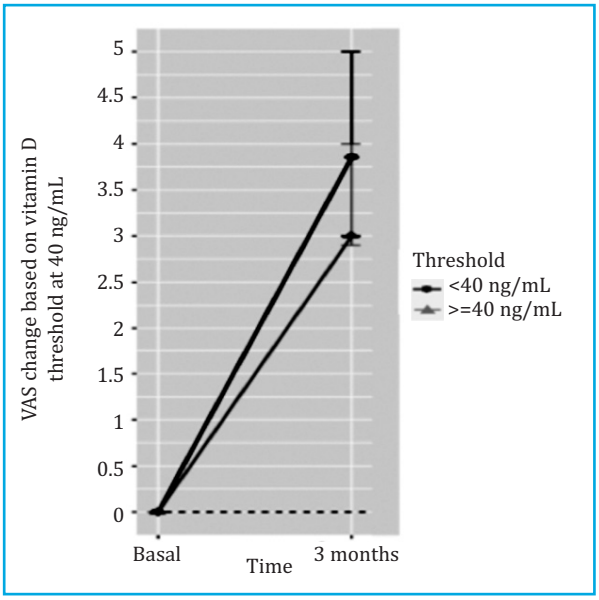


Table 4. Mean BMD values and its percentage change from baseline to 12 months of AI treatment

Location BMD	n	Basal	12 months	% mean change [95% CI]
Lumbar spine	472	0.970 ± 0.112	0.955 ± 0.112	-1.52 [-1.83; -1.20]*
Neck of the femur	473	0.755 ± 0.090	0.746 ± 0.090	-1.13 [-1.53; -0.73]*
Total hip	471	0.902 ± 0.097	0.896 ± 0.097	-0.61 [-0.93; -0.28]*

BMD: bone mineral density; CI: confidence interval. In the t test, the significant differences between BMD values at baseline and at 12 months are indicated in *(p<0.001).

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Humeral fragility fractures in a tertiary referral hospital. Clinical and epidemiological characteristics

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Summary

Introduction and objetives: Humeral fragility fractures represent an important complication of osteoporosis as they rank the third most prevalent in individuals over sixty years old. Our study aims to analyze the prevalence and treatment of the humeral fragility fractures in a tertiary referral hospital.

Patients and methods: Retrospective study of those patients presenting humeral fragility fractures who attended a tertiary referral hospital during 2013.
Clinical and epidemiological variables were collected, and the incidence of new fractures and that of mortality was analyzed over a three-year period.

Results: 248 humeral fragility fractures were analyzed. 81% of the patients were women whose average age was 71 years. 28.2% of the patients have suffered a previous fracture and 20.2% of them suffered one at a later time. 12.5% had been previously diagnosed with osteoporosis and only 9.2% got this bone metabolic condition diagnosed after fracturing the humerus. 18% of patients passed away during the follow-up period.

Conclusion: In our area of expertise, humeral fragility fractures are followed by a low percentage of underlying osteoporosis cases being diagnosed and treated, what may be the trigger to a rise in the risk of new fractures.

Key words: humeral fracture, osteoporosis, mortality.

Introduction

The humeral fragility fracture is an important consequence of osteoporosis. It constitutes 5% of all osteoporotic fractures and is the third most frequent non-vertebral fracture in individuals over 60 years of age after hip fractures and those of the distal radius[1]. Compared with the general population, patients with a proximal humeral fracture present a higher mortality rate in the first year, the risk being five times higher during the first month after the fracture[2].

Several studies have been published into the risk factors linked to vertebral or hip fractures while the lack of studies about humeral fractures as indicators of osteoporosis stands out. Thus, in the Reykjavik Study Fracture Register, 9,504 osteoporotic fractures were analyzed and 3,616 patients who showed new major fragility fractures were screened. This led the researchers to propose that the risk of suffering a recurring fracture changed according to age, gender and the place where the previous fracture was located, therefore posing a higher risk of suffering vertebral and hip fractures than that of humeral or wrist fracture[3]. Humeral fracture is not usually related to osteoporosis in standard clinical practice. So a limited of antiosteoporotic drugs are prescribed post fracture, as some retrospective studies report[4,5].

The aim of the present study was to analyze the clinical and epidemiological characteristics, and management, of the patients presenting humeral fragility fractures and the incidence of new clinical fractures. We also report their mortality rate over the three-year follow-up period.

Patients and methods

A retrospective and descriptive cohort study was carried out of all patients aged 45 or over, diagnosed with humeral fragility fractures at the Marqués de Valdecilla University Hospital (HUMV) during 2013. It is a tertiary referral university hospital assisting a population of 350,000 inhabitants in Cantabria. Humeral fractures were identified through the center's Clinical Documentation and Admission Service database, using the code CIE9-MC 812 (812.0; 812.1; 812.2; 812.3). In addition, a follow-up of the cases was carried out, through medical records, from the moment of the humeral fracture until December 31, 2016, to analyze the development of new fractures and all-cause mortality.

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Initially 337 patients with humeral fractures were identified. Of this group, 89 were excluded from the analysis because they presented high-energy traumatic fractures (n=79) or because of the absence or loss of clinical data in the first episode or during follow-up (n=10).

The following variables were analyzed: age, gender, age at menopause, body mass index (BMI) (kg/m^2), smoking habit (smoker, non-smoker or ex-smoker), alcohol habit (consumption of more than 30 g of ethanol per day, less than 30 g or ex-drinker), diseases with influence over or related to bone metabolism (hyperthyroidism, hyperparathyroidism, malabsorptive syndromes such as celiac disease or inflammatory bowel diseases, rheumatoid arthritis, metastatic neoplastic disease or hematological neoplasms), chronic treatment with corticosteroids (≥7.5 mg per day for more than 3 months), risk factors associated with falls, both intrinsic (visual, gait and balance disturbances) and extrinsic (use of benzodiazepines or hypotensive drugs), existence of previous fractures unrelated to the skull or face (vertebral fracture, in the hip, radius or other locations), existence of previous multiple fractures, history of hip fracture in a first-degree relative or, previous diagnosis of osteoporosis, previous treatment for osteoporosis (calcium and vitamin D supplements, bisphosphonates, selective estrogen receptor modulators -SERM-, teriparatide, denosumab, strontium ranelate), date of the humeral fracture, location of the humeral fracture (proximal or diaphyseal), treatment of the fracture (surgical or orthopedic), subsequent diagnosis of osteoporosis, performance of bone densitometry and result if affirmative (bone mineral density -BMD- in g/cm^2 and T index), subsequent treatment for osteoporosis, new fractures after the humeral fracture (vertebral fracture, in the hip, radius or other locations), refracture of the same humerus, and finally, death within 3 years after the initial fracture and date of the same.

For the statistical data analysis, a descriptive study was carried out. Qualitative variables were expressed as frequencies, number and percentage, and quantitative variables as mean and standard deviation (SD). The data were collected anonymously through an individualized registration code. A level of $p<0.05$ was considered significant.

Results

248 patients with humeral fragility fractures were included in the analysis. Table 1 summarizes the main clinical and epidemiological characteristics of the cases analyzed.

The mean age was about 71 years and 81% of the fractures occurred in women. The mean age at menopause was 49 years and the mean BMI was 28 kg/m^2, indicator of overweight.

It should be noted that a high percentage of the patients took drugs associated with an increased risk of falls, benzodiazepines being the most common, followed by antihypertensive drugs. Diseases with an effect on bone metabolism were also evaluated, finding that 11% suffered from any of them.

Almost a third of the patients had suffered previous fractures (excluding skull, facial, or hand and foot fractures), the most frequent being those of the hip and the distal radius. In addition, about 14% had presented frac-

Table 1. Clinical and epidemiological characteristics of patients with humeral fragility fractures (n=248)

Variable	N (%)
Age *(years), mean ± SD*	70.9 ± 14.4
Women	201 (81)
Age at menopause (years), *mean ± SD*	48.5 ± 4.8
Body mass index *(kg/m^2), mean ± SD*	28 ± 5.7
Active smoking	44 (18)
Alcohol consumption >30 g/day	39 (16)
Benzodiazepine use	74 (29.8)
Chronic corticosteroid therapy	8 (3.2)
Diseases related to bone metabolism:	28 (11.3)
- Hyperthyroidism	8 (28.6)
- Metastatic disease	6 (21.4)
- Malabsorptive syndromes	5 (17.9)
- Rheumatoid arthritis	5 (17.9)
Intrinsic risk factors for falls:	82 (33.0)
- Visual disturbance	10 (12.2)
- Altered gait and balance	72 (87.8)
Previous fractures:	69 (28.2)
- Hips	15 (19.5)
- Vertebral	4 (5.2)
- Colles fracture	7 (9.1)
- Other locations	43 (66.2)
- More than one fracture	34 (13.7)
Patients with previous antiosteoporotic treatment	31 (12.5)
Patients with calcium and vitamin D supplements	25 (10)

tures in more than one location. It is noteworthy that in only 0.4% of the cases' medical history a hip fracture in a first-degree relative was registered.

Table 2 shows the management of patients with humeral fracture and the follow-up variables analyzed. During this follow-up period, one fifth suffered a new fracture and about 18% died within 3 years after the initial humeral fracture.

The changes in antiosteoporotic treatments after humeral fracture are shown in table 3. 31 patients had a previous diagnosis of osteoporosis and had received treatment, 23 patients had been treated with bisphosphonates, 3 with denosumab, 2 with teriparatide, 2 with strontium ranelate and 1 with a SERM. It is worth noting that out of the 31 patients previously treated for osteoporosis, in 17 of them (more than half) it was interrupted or not restarted after the humeral fracture. It was observed that in 7 patients who had received a treatment with oral bisphosphonates for 10 years, it was suspended, without restarting, after suffering the humeral fracture. In addition, 2 patients under treatment with bisphosphonates died during follow-up, 1 patient had received full treatment with teriparatide for two years, and 1 patient had been treated for one year with denosumab without specifying the reason for its suspension. In 6 patients, the reason why the previous treatment had been suspended was not reflected. In none of these 17 patients was the need to initiate treatment for osteoporosis raised in their medical records at the time of the humeral fracture despite being all of them diagnosed with osteoporosis.

Treatment was restarted after the humeral fracture in 20 patients (12 with bisphosphonates, 6 with denosumab and 2 with teriparatide). Besides, calcium in combination with vitamin D was prescribed to 46 patients.

Discussion

We have analyzed a retrospective cohort of 248 patients with humeral fragility fracture, who had a 3-year follow-up. After the humeral fracture, a low percentage of them were diagnosed and treated for underlying osteoporosis.

Table 2. Follow-up and subsequent management of patients with humeral fragility fractures (n=248)

Variable	N (%)
Proximal humeral fracture	220 (88.7)
Orthopedic treatment	143 (57.7)
Patients with antiosteoporotic treatment after humeral fracture:	34 (13.7)
- Patients with de novo started treatment	20 (9.2)
Patients with calcium and vitamin D supplements	46 (18.5)
Posterior fractures:	50 (20.2)
- Hips	15 (30.0)
- Vertebral	13 (26.0)
- Colles fracture	5 (10.0)
- Other locations	17 (34.0)
- More than one fracture	5 (2.0)
Humeral refracture	3 (1.2)
Death during the 3 years of follow-up	44 (17.7)

Table 3. Changes in antiosteoporotic treatment in patients previously diagnosed with osteoporosis and initial treatment in patients without a prior diagnosis

Previous treatment	Post treatment	N*
Bisphosphonates	Bisphosphonates	8
Bisphosphonates	Teriparatide	1
Bisphosphonates	-	14
SERM	-	1
Teriparatide	Denosumab	1
Teriparatide	-	1
Denosumab	Denosumab	2
Denosumab	-	1
Strontium	Teriparatide	1
Strontium	SERM	1
-	Bisphosphonates	12
-	Denosumab	6
-	Teriparatide	2

*: number of patients receiving treatment before and after the humeral fracture; SERM: selective estrogen receptor modulators.

More than 80% of all humeral fractures occurred in women. In this sense, Chu et al.[6] observed that humerus fractures are 3 to 4 times more common in women, findings similar to those published by Clinton et al.[7] The patients' mean age (71 years) is similar to that published in previous studies reporting age ranges between 64 and 79 years[8-11].

Mean BMI of 28 kg/m^2 describes an overweight population. This is an interesting fact, since overweight and obesity represent a risk factor for suffering a humeral fracture, but their relation with other osteoporotic fractures, such as that of the hip, is less clear as hip fractures are usually linked to low weight[12]. Regarding toxic habits, nearly 20% of the patients were active smokers and consumed more than 30 g of ethanol per day (maximum limit recommended by the World Health Organization in men, being 20 g that in women). These proportions were very similar to the 28% and 15%, respectively, reported by Roux et al.[13], which highlights the need to spend time and resources on promoting health and healthy habits as a fundamental part of the treatment of osteoporosis.

Regarding the consumption of drugs at the time of the humeral fracture, the high percentage of people under treatment with benzodiazepines is surprising. This pharmacological group is widely prescribed in standard practice, and its use has been related to an increased risk of falls, and consequently, of fractures[14].

A relevant percentage of patients with humeral fractures, nearly a third, had already presented a previous fracture and 20% suffered a subsequent fracture. In terms of distribution, 15 patients had already had a hip fracture, while another 15 had a hip fracture in the follow-up period. 47% of these occurred during the first year after the initial humeral fracture. About this, Clinton et al.[7] have reported that a fracture of the proximal limb of the humerus increases the risk of hip fracture in more than 5 times during the first year, but it does not seem to be linked to a significant increase in subsequent years. These data are interesting since the humeral fracture is presented as an opportunity to optimize prevention of subsequent fractures in these patients.

Treatment and diagnosis of osteoporosis prior to the humeral fracture was limited (12.5%). This figure is consistent with the 19% published by Piple et al.[4], who studied a retrospective cohort of 1,700 patients aged 50 or over with humeral fracture between 2008 and 2014. However, it should be emphasized that only 20 of the 217 of our patients who did not receive antiosteoporotic treatment, 9.2%, were diagnosed with osteoporosis and treated after the initial humeral fracture. This percentage is somewhat higher than the 5.5% reported in a retrospective national study in which 11,609 patients aged 50 or over with a humeral fracture were analyzed[5]. This reflects that, in standard clinical practice, this type of fracture continues to be a poorly considered entity when it comes to prescribing a treatment for osteoporosis. Furthermore, it is far behind other major fractures, such as vertebral or hip fractures, which are also often undertreated[5,15].

Regarding mortality, in a study carried out in patients over 16 years of age presenting humeral fractures, an even greater risk of mortality in men was observed than that reported after a hip fracture[16]. We cannot compare these data with our study as the age group and the gender distribution were different. A study carried out in Korea in individuals over 50 years of age with a proximal humeral fracture during the period 2008-2012, showed an annual percentage of mortality in men of between 8.5% and 10.8%, and in women of between 6.4% and 7%[17].

Limitations of the study are its retrospective design, the study scope restricted to a single center, the lack of data into the causes of mortality and the influence of comorbidities on it.

In conclusion, humeral fragility fractures are followed, in our field of expertise, by a low percentage of diagnosis and treatment for underlying osteoporosis, which may trigger an increased risk of new fractures. The humeral fragility fracture is a major osteoporotic fracture and specific antiosteoporotic treatment should be initiated to minimize it.

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

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Calcium and vitamin D supplementation in the management of osteoporosis. What is the advisable dose of vitamin D?

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Summary
The pathophysiological foundations justifying calcium and vitamin D supplements in osteoporosis are supported by extensive scientific evidence that has been obtained through several randomized clinical trials and subsequent meta-analyzes that have shown a statistically significant and clinically relevant reduction in the risk of osteoporotic fractures. This evidence has led to its recommendation by several scientific societies interested in the management of osteoporosis.
In order to optimize the efficacy and the benefit/risk balance of these, calcium and vitamin D should be administered together with the drugs that are prescribed for the treatment of osteoporosis, since calcium and vitamin D have been used in all these reference studies, both in the arm that receives the drug and also in the placebo arm. The most commonly used calcium salt is carbonate and the metabolite of vitamin D, cholecalciferol or vitamin D_3.
There is no consensus or conclusive scientific evidence on the dose to be used in vitamin D deficiency associated with osteoporosis. However, the trend has always been to increase these amounts, from the 400 IU recommended 30 years ago to the 2,000 IU daily today. We will review in this article which recommendations are made by means of the clinical guidelines, as they collect the available scientific evidence.

Rationale for using calcium and vitamin D in osteoporosis

Osteoporosis is the most common bone metabolism disease[1] and is characterized by a significant decrease in bone mineral density that is accompanied by alterations in the microarchitecture of the bone, which results in increased skeletal fragility and, consequently, an increase risk of fractures[2]. Clearly related to aging, its prevalence, which in women between 50 and 59 years of age has been estimated at 4%, increases to 52% in women older than 80 years[2]. Hip fracture in osteoporotic women produces an increase in mortality over the first two years post-fracture of between 12 and 20%, and more than 50% of survivors are not able to return to an independent life, many of them requiring long-term home help[3].

Calcium is a mineral-type nutrient that plays key roles in human physiology. In relation to bone, it is a basic constituent of calcium hydroxyapatite crystals, a form that contains 99% of the body's calcium and a fundamental component of bones and teeth. Insufficient calcium accumulation leads to low bone mineralization and a decrease in peak bone mass, this being one of the key factors for the appearance of osteoporosis and associated osteoporotic fractures. In this sense, bone tissue acts as a calcium reservoir to guarantee the efficiency of all these physiological processes, regulating its exit from the bone through the bone remodeling process[4].

Furthermore, vitamin D, hormone D, or 1,25 $(OH)_2$ D (1,25 dihydroxycholecalciferol, or calcitriol) facilitates the intestinal absorption of calcium by regulating calcium transport proteins and the consequent promotion of transport of transcellular calcium at the level of the intestine[5]. The main function of the endocrine system of vitamin D at the bone level is to preserve serum calcium homeostasis. Therefore, vitamin D deficiency causes secondary hyperparathyroidism that normalizes serum calcium through increased renal synthesis of hormone D from its immediate precursor, calcidiol or 25 (OH) D (25-hydroxy cholecalciferol), increasing both the intestinal absorption of dietary calcium as compensatory bone resorption at the expense of increased bone turnover and consequent loss of bone mass[5]. Even moderate vitamin D deficiency can promote age-mediated physiological bone loss and thus accelerate the pathophysiological process of osteoporosis, significantly increasing the risk of osteoporotic fragility fractures[6]. Furthermore, the important impact of vitamin D on muscle biology cannot be ignored, since it has been observed that the increased risk of falls associated with hypovitaminosis D may lead to an increased risk of osteoporotic fractures[5].

Calcium and vitamin D in randomized clinical trials and meta-analyzes

Meta-analysis with positive results

We have several meta-analyzes carried out with the many randomized, double-blind, placebo-controlled clinical trials (RCTs) in the treatment of osteoporosis. The

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vast majority of these studies have been carried out with calcium carbonate and with cholecalciferol as the metabolite of vitamin D, and, therefore, the most physiological form[7], in patients with different levels of risk of osteoporosis and, even some of them, with objectively diagnosed osteoporosis.

Most of the meta-analyzes of these RCTs have shown a reduction in the risk of fractures, both vertebral and non-vertebral, including hip fractures, the latter undoubtedly the most relevant from the point of view of morbidity and mortality and social health impact. As many of the RCTs mentioned were carried out in the 1980s and nineties, with perhaps different clinical research methodologies in bone mineral metabolism, we have focused our review mainly on the most recent meta-analyzes, that is, those published in the last decade.

Thus, in 2014 the data of a systematic review carried out according to the Cochrane methodology on the role of vitamin D in the prevention of fractures in postmenopausal women and elderly men were published. This work included data from 91,791 patients (including non-institutionalized, institutionalized, and even hospitalized) with different risks of osteoporotic fracture, from 53 RCTs. Selected 10 RCTs (n=49,976) in which joint supplementation of calcium and vitamin D was used (the majority carried out with cholecalciferol as the form of vitamin D used), the researchers concluded that calcium and vitamin D reduced the risk of fracture statistically significant (RR: 0.95; 95% CI –95% confidence interval–: 0.90-0.99). Furthermore, by type of fracture –good quality evidence again– they found statistically significant risk reductions for both hip fracture (9 RCTs; n=49,853; RR: 0.84; 95% CI: 0.73-0.96), as for other non-vertebral fractures (8 RCTs; n=10,380; RR: 0.86; 95% CI: 0.78-0.96). The analysis did not detect a statistically significant risk reduction associated with treatment with calcium and vitamin D in relation to vertebral fractures[8], although it is known that this type of osteoporotic fracture usually has a better prognosis and fewer complications than the previous ones, sometimes even asymptomatically.

That same year, Bolland and Reid's research group in New Zealand, well known in the field of bone mineral metabolism for their unfavorable opinion of the need for calcium and vitamin D supplementation, published a sequential meta-analysis. In this paper, along with other extra-osseous health parameters, they analyzed the reduction in fracture risk appearance. According to their cut-off point of minimum risk reduction of 15% as a clinically significant limit, they did not find treatment with calcium and vitamin D relevant in reducing the risk of total fractures or hip fracture. However, according to the results of their own analysis, statistical significance was reached in total fractures, with a risk reduction of 8% (RR: 0.92; 95% CI: 0.85-0.99), and even more so in hip fracture, with a risk reduction that reached 16% (RR: 0.84; 95% CI: 0.74-0.96; p=0.009)[9].

Another study was carried out with the support of the US NOF (National Osteoporosis Foundation), encompassing data from 30,970 individuals grouped in a total of 8 RCTs to analyze effects on the incidence of total fractures and 6 RCTs regarding only hip fracture. The results pointed to a positive effect of calcium and vitamin D treatment, again cholecalciferol in almost all RCTs, achieving a risk reduction of 14% (RR: 0.86; 95% CI: 0.75-0.98) for total fractures, and with a robust risk reduction of up to 39% (95% CI: 0.46-0.82) for hip fractures[10,11].

Finally, 3 studies with positive results have recently been published: a meta-analysis of 6 RCTs grouping data from 49,282 patients that yielded a discrete, albeit statistically significant, risk reduction in favor of the combined calcium/vitamin D treatment of 6% of total fractures (RR: 0.94; 95% CI: 0.89-0.99), and more relevant in terms of hip fracture, reaching a 16% risk reduction (RR: 0.84; 95% CI % 0.72-0.97)[12]. Another that analyzed data from up to 47 RCTs (n=58,424) found a statistically significant reduction in risk of falls of 0.88 (95% CI: 0.821-0.945; p<0.01) for cholecalciferol and calcium and, additionally, reduction risk of total fractures of 0.85 (95% CI: 0.741-0.996; p=0.045)[13]. A third meta-analysis also concluded significant reductions in the risk of osteoporotic fractures, both total and hip[14]. Table 1 shows a summary of the results of the aforementioned meta-analyzes.

Meta-analysis with negative results

Probably the work with the greatest impact in this regard was that published by the group by Zhao et al., who carried out a meta-analysis with data from 33 RCTs that included 51,145 non-institutionalized adults over 50 years of age at risk of fracture. These investigators did not find statistically significant risk reductions from the combination of calcium and vitamin D in hip fractures (RR: 1.09; 95% CI: 0.85-1.39) or in other non-vertebral fractures (RR: 0.88; 95% CI: 0.75-1.03); neither in vertebral fractures (RR: 0.63; 95% CI: 0.29-1.40), nor in total fractures (RR: 0.90; 95% CI: 0.78-1.04)[15]. This meta-analysis has subsequently received some criticism, as it could have had some methodological biases such as: 1) the exclusion of RCTs of institutionalized patients, usually at higher risk of fracture than non-institutionalized patients and with lower 25(OH)D levels and, therefore, more sensitive to the effect of supplementation; 2) the inclusion of numerous RCTs with treatment follow-ups too short (less than 12 months) to detect positive effects; 3) the fact that in one of the most important RCTs included for data analysis (known as the WHI study –Women's Health Initiative–) adherence to supplementation was notably low[16]; and 4) the inclusion of several RCTs in which the form of vitamin D supplementation was by oral or intramuscular bolus mega-doses, which have been clearly relegated from routine clinical practice due to their demonstrated negative effect of increasing the risk of falls and fractures[17].

Along the same lines, in 2019, another meta-analysis from another research group was published with also negative results[18]. In this meta-analysis, some of the methods criticized in the previous work were repeated, such as the non-inclusion of RCTs with institutionalized patients, as well as the inclusion of RCTs in which mega-doses of vitamin D were used.

Calcium and vitamin D in combination with drugs used in the treatment of osteoporosis and clinical guidelines

The evidence on the need to combine these drugs

Apart from the intrinsic activity of calcium and vitamin D supplementation in the prevention of osteoporotic fractures, it should be noted that the large RCTs carried out for the regulatory approval of the drugs we use for the treatment of osteoporosis have been carried out by admi-

Table 1. Summary of calcium and vitamin D meta-analyzes with positive results

First author and reference	Patients included	RR non-vertebral fracture	RR hip fracture	RR total fractures
Avenell[8]	91,791	14% [0.86 (0.78-0.96)]	16% [0.84 (0.73-0.96)]	5% [0.95 (0.90-0.99)]
Bolland[9]	76,497	N/A	16% [0.84 (0.74-0.96)]	8% [0.92 (0.85-0.99)]
Weaver[10,11]	30,970	N/A	39% [0.61 (0.46-0.82)]	14% [0.86 (0.75-0.98)]
Yao[12]	49,282	N/A	16% [0.84 (0.72-0.97)]	6% [0.94 (0.89-0.99)]
Thanapluetiwong[13]	58,424	N/A	15% [0.85 (0.74-0.99]	NS
Eleni[14]	74,325	N/A	39% [0.61 (0.40-0.92)]	26% [0.74 (0.58-0.94)]

N/A: data not available; NS: not statistically significant; RR: risk reduction.

nistering to all patients calcium and vitamin D supplements. Regardless of the pharmacological class, whether they are bisphosphonates, PTH analogues, RANK ligand inhibitors or any other mechanisms of action, it is of great importance that these drugs are accompanied by calcium and vitamin D so that they can produce an optimal benefit/risk balance in patients with osteoporosis.

The form of vitamin D used to accompany these anti-osteoporotic drugs in their respective reference RCTs was always cholecalciferol, and none of them used intermediate vitamin D metabolites such as calcifediol, nor hormone D (calcitriol)[19]. A summary of the different reference studies can be seen in table 2.

Recommendations of the clinical guidelines of the societies interested in osteoporosis

As far as Spain is concerned, the Spanish Society of Rheumatology (SER)[29], the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM)[30], the Spanish Society of Endocrinology and Nutrition (SEEN)[31], the SEMFYC (Spanish Society of Family and Community Medicine – rheumatological diseases working group)[32] or the Spanish Association for the Study of Menopause (AEEM)[33], just to mention some of those that we have found most relevant, recommend the use of calcium and vitamin D supplements in the therapeutic management of osteoporosis of different origin.

Similarly, at the international level, it is recommended by the following societies: European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO) in conjunction with the advisory committees and national societies of the International Osteoporosis Foundation (IOF)[34]; British National Osteoporosis Guideline Group (NOGG)[35]; National Osteoporosis Foundation (NOF)[36], and the joint American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE)[3] in the USA; and Endocrine Society (ES), together with the European Society of Endocrinology (ESE)[37].

In table 3 we summarize the recommendations made by the scientific societies mentioned above on the supplementation of calcium and, especially, vitamin D.

Despite the fact that these scientific societies recommend the joint administration of calcium and vitamin D with the indicated treatment for osteoporosis, it is surprising and at the same time worrying that in our country there is still a significant proportion of patients, close to 40%, who start treatments for osteoporosis without the accompaniment of supplementation with calcium and vitamin D[38].

Drugs of choice and future dosage trends

Although it seems quite evident that patients with osteoporosis and vitamin D deficiency should be treated with calcium and vitamin D, it is also true that there is no solid scientific evidence and, therefore, no consensus among scientific societies, regarding the dose to use. However, there is a clear trend in this regard:

Calcium

The most widely used form of calcium in our country is undoubtedly calcium carbonate[39], a calcium salt with greater bio-availability of element calcium than others also available, but less common, such as calcium citrate[40].

As for the appropriate amounts of calcium in the context of osteoporosis, since 2010 the most replicated and internationally accepted reference is the Food and Nutrition Board of the Institute of Medicine (IOM) guideline of the United States which recommends a daily intake (contained in the diet or through exogenous supplementation when the above is not possible) of 1,200 mg of calcium for men over 70 years old or women over 51 years old[4]. Unfortunately, the majority of the population at risk of osteoporosis do not ingest the 1,200 mg/day recommended by the IOM. This has recently been verified in the epidemiological study ANIBES (Anthropometry, Intake and Energy Balance in Spain), published in 2017. Carried out through surveys on nutritional habits of more than 2,000 individuals of a very wide age range in our country, it estimated that the average daily amounts of calcium ingested through the diet of women and men older than 65 years were 662 and 629 mg, respectively[41]. Therefore, if we were to reach the IOM guideline, we would have to supplement with about 600 mg of calcium daily in the form of exogenous calcium carbonate supplement to reach 1,200 mg/day.

Vitamin D

Cholecalciferol is the form of vitamin D most used in RCTs and therefore the metabolite specifically recommended in most of the aforementioned published clinical guidelines on the management of osteoporosis. We do not have conclusive scientific evidence that establishes the recommended daily doses in the treatment of osteoporosis in a consensual way. It is possible that the trend is to increase the daily 800-1,000 IU of vitamin D that is used mostly in routine clinical practice at higher doses, since this has been the norm up to now in the design of clinical trials.

Table 2. Reference studies of drugs used for the treatment of osteoporosis. Dose of vitamin D (cholecalciferol) used

Drug	Year of publication	Study acronym	First author	Cholecalciferol (dose in IU)	Bibliographic reference
Alendronate	2000	FIT	Black	250	20
Risedronate	1999	VERT	Harris	500	21
Ibandronate	2004	BONE	Delmas	400	22
Zoledronate	2007	HORIZON	Black	400-1,200	23
Raloxifen	1999	MORE	Ettinger	400-600	24
Calcitonin	2000	PROOF	Chesnut	400	25
Teriparatide	2001		Neer	400-1,200	26
Denosumab	2009	FREEDOM	Cummings	400-800	27
Romosozumab	2016	FRAME	Cosman	50,000-60,000 initially; subsequently 600-800 IU	28

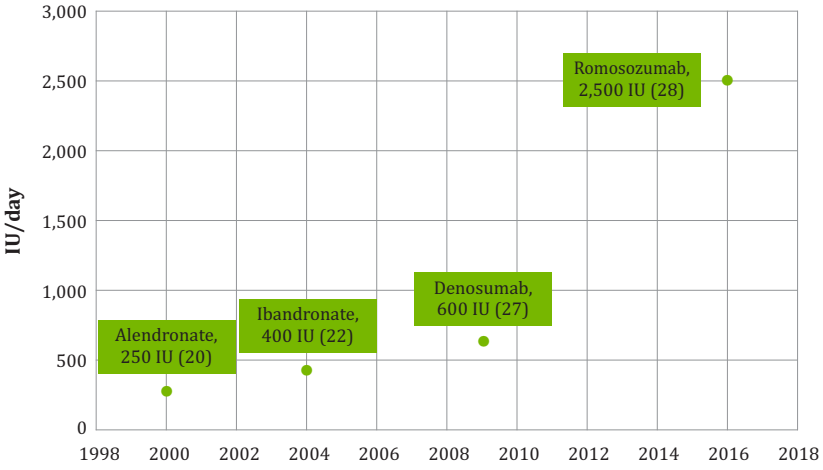
Table 3. List of recently published guidelines from national and international scientific societies specialized in the clinical management of osteoporosis that recommend supplementation with calcium and vitamin D

Scientific society	Geographical scope	Year of publication	Vitamin D. Drug and dose in IU	Bibliographic reference
Spanish Society of Rheumatology (SER)	Spain	2019	NE 800	29
Spanish Society for Bone Research and Mineral Metabolism (SEIOMM)[30]	Spain	2015	NE 800-1,000	30
Spanish Society of Endocrinology and Nutrition (SEEN)	Spain	2015	NE Variable according to type of osteoporosis	31
Spanish Society of Family and Community Medicine (SEMFYC)	Spain	2014	NE 800	32
Spanish Association for the Management of Menopause (AEMM)	Spain	2012	NE 800	33
European Society for Clinical and Economic Aspects of Osteoporosis (ESCEO)/International Osteoporosis Foundation (IOF)	Global	2019	Cholecalciferol 800	34
National Osteoporosis Guideline Group (NOGG)	Great Britain	2017	Cholecalciferol 800	35
National Osteoporosis Foundation (NOF)	EE.UU.	2014	Cholecalciferol 800-1,000	36
American Association of Clinical Endocrinologists/ American College of Endocrinology (AACE/ACE)	EE.UU.	2016	Cholecalciferol 1,000-2,000	3
Endocrine Society/European Society of Endocrinology (ES/ESE)		2019	NE Unspecified dose	37

NE: vitamin D with unspecified drug.

Thus, more than 30 years ago, the reference trials with alendronate were designed with a supplement of vitamin D of 250 IU/day[20], an amount that increased 4 years later to 400 IU/day with ibandronate[22], and by 2009 reached 800 cholecalciferol IU/day in patients with baseline 25(OH) D levels of 12-20 ng/ml or 400 IU/day for levels greater than 20 ng/ml in the FREEDOM study with denosumab[27] (average in the first month of 600 IU/day treatment). Thus, we observe that this upward trend is consolidated in the most recent reference study with romosozumab, published in 2016, and in whose design a loading dose of 50,000-60,000 IU/day of cholecalciferol was established (the use of vitamin D_2 or ergocalciferol was also allowed) and then daily doses of 600-800 IU for patients with baseline levels of 25 (OH) D between 20 and 40 ng/ml[28], which would mean an average in the first month of treatment of about 2,500 IU/day (see figure 1).

Figure 1. Evolution of the daily doses of the first month of treatment (IU/day) of cholecalciferol associated with anti-osteoporotic drugs. Year of publication, anti-osteoporotic drug, dose and bibliographic reference (in parentheses) are indicated



In our opinion, it would be advisable to transfer this trend of increasing the dose of cholecalciferol in drugs under development to our usual clinical practice of supplementation in patients with vitamin D deficiency and osteoporosis. Similarly, some renowned scientific societies, in their clinical guidelines and consensus documents, recommend a supplementation of up to 2,000 IU/day of cholecalciferol in patients with osteoporosis. Among these groups, the International Osteoporosis Foundation (IOF)[42], the Endocrine Society (ES)[43] or the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE)[3] stand out.

We will be better able to reach the optimal levels of 25(OH)D higher than 30 ng/ml widely recommended by the main scientific societies which manage osteoporosis if we treat patients with 2,000 IU/day than if we treat them only with 800-1,000 IU/day, and that this can produce an additional clinical benefit in osteoporosis. In fact, there are already studies that provide some evidence that this could be the case. The Zurich Hip Fracture Trial carried out by the Dawson-Hugues and Bischoff-Ferrari groups, a clinical trial in which it was compared in a bi-factorial way the administration of 2,000 IU/day or 800 IU/day of cholecalciferol to 173 patients who had suffered a hip fracture, in combination or not with a physical exercise program for 12 months, concluding that the administration of 2,000 IU/day was associated to a more limited deterioration in the quality of life between months 6 and 12, evaluated by means of the EuroQol EQ-5D-3L scale scores[44]; also, a systematic review of the literature that analyzed 12 publications on different guidelines for supplementation with cholecalciferol in menopausal women at risk of osteoporosis with vitamin D deficiency, in which the authors observed that only daily doses of 2,000 IU/day increased 25 (OH) D levels consistently above 30 ng/ml[45].

CONCLUSION

To date, scientific evidence confirms the need to treat all patients with osteoporosis and vitamin D deficiency with calcium and vitamin D (preferably cholecalciferol), regardless of their other osteoporosis treatment. The daily doses of cholecalciferol to be used should reach at least 2,000 IU.

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SEIOMM recommendations on the prevention and treatment of vitamin D deficiency

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Summary

Objetive: Provide evidence-based recommendations for preventing and treating vitamin D deficiency .
Methods: A multidisciplinary working group made up of 10 members of the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM), formulated the clinical questions of interest. Subsequently, a systematic review of the literature was carried out in MEDLINE (PubMed), EMBASE and Cochrane on the available evidence for each of the questions posed. Articles published in English or Spanish between July 15, 2016 and December 31, 2020 were included. To establish the strength of the recommendations and the degree of evidence, the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used. After the formulation of the recommendations, these were discussed jointly in the working group and ratified by all SEIOMM members.
Results and conclusions: This document establishes a series of recommendations on optimal concentrations and screening for 25-hydroxyvitamin D deficiency, vitamin D requirements in different populations, sun exposure and supplementation strategies in patients with deficiency.

Key words: vitamin D, nutrition, 25-hydroxyvitamin D, osteoporosis, fracture, cholecalciferol, calcifediol.

1. Introduction

Since its discovery, a century ago, we have advanced in the knowledge of what was erroneously called "vitamin" D. We now know that it is not a vitamin, but we continue to call it that out of custom and tacit consensus. In fact, it is an endocrine system, the vitamin D endocrine system (VDES), similar to that of other steroid hormones. Cholecalciferol or "vitamin" D3, is the threshold (physiological) nutrient of the system, synthesized from 7-dehydrocholesterol in the skin, by the action of ultraviolet B (UVB) solar radiation. This route represents about 80-90% of the contribution to the body, the rest is obtained from the diet (10-20%)[1]. There is another isoform, of nutritional contribution, called ergocalciferol or "vitamin" D2 that is found in small quantities in foods of vegetable origin, yeasts and fungi, not commonly used in Spain[2,3].

Both cholecalciferol and ergocalciferol are biologically inactive precursors, requiring metabolic modifications to activate the hormonal function of the system. Through the action of the liver enzyme 25-hydroxylase (CYP2R1/CYP27A1 and others), the hydroxylation of cholecalciferol and ergocalciferol occurs to form 25-hydroxyvitamin D_3 (caldidiol or calcifediol) and 25-hydroxyvitamin D_2 (ercalcidiol), respectively. 25-hydroxyvitamin D (sum of 25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3) has a long half-life (2-3 weeks) and it is the prohormone. It is the prohormone of VDES. It's measurement is used as a marker of the nutritional status of the system.

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1,25-dihydroxyvitamin D_3 is the substrate for the synthesis of 1,25 (OH) $_2D_3$ or calcitriol by the action of 1-α-hydroxylase (CYP27B1) in the kidney for its endocrine actions, and in cells of multiple tissues, organs and systems, such as skin, parathyroid gland, breast, colon, prostate, lung, as well as cells of the immune system and bone, for their auto/paracrine actions. Calcitriol is the hormone of the system and has a very short half-life (5-8 hours).

1-α-hydroxylase in the kidney is regulated, through a feedback mechanism, by parathyroid hormone (PTH), the increase of which leads to an increase in the production of calcitriol, which, in turn, inhibits the production of PTH. Hypophosphatemia and fibroblast growth factor 23 (FGF23) also regulate 1-α-hydroxylase, increasing and decreasing the production of calcitriol, respectively.

The binding of calcitriol to the vitamin D receptor (VDR), a nuclear transcription factor present in cells of multiple organs, determines the systemic and auto/paracrine endocrine action of VDES (Figures 1 and 2).

The system uses the enzyme 24-α-hydroxylase (CYP24A1), both in the kidney (through endocrine control) and in other cells and tissues, to form the inactive metabolites 24,25-dihydroxyvitamin D and 1,24,25-trihydroxyvitamin D, from 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D respectively, which are derived after several oxidations in calcitroic acid, and other glucuronic or sulfate metabolites that are eliminated mainly by the bile, constituting an important catabolic regulation system of the metabolism of VDS.

In the blood, the metabolites of VDES are transported 88% by the transporter protein of vitamin D (DBP), and 10% by albumin, circulating only 1-2% in free form[4].

The main action of VDES, through calcitriol, is the regulation of calcium and phosphorus homeostasis and skeletal mineralization, and it does so in 4 organs: mainly in the intestine, facilitating the absorption of calcium and phosphorus; kidney, increasing the tubular reabsorption of both; parathyroids, inhibiting PTH secretion; and bone, regulating the differentiation of osteoclasts and osteoblasts and the production of mineralization regulating proteins such as osteopontin and osteocalcin[5].

Sustained vitamin D deficiency has been associated with growth retardation and rickets in children, and osteomalacia and osteoporosis in adults[6].

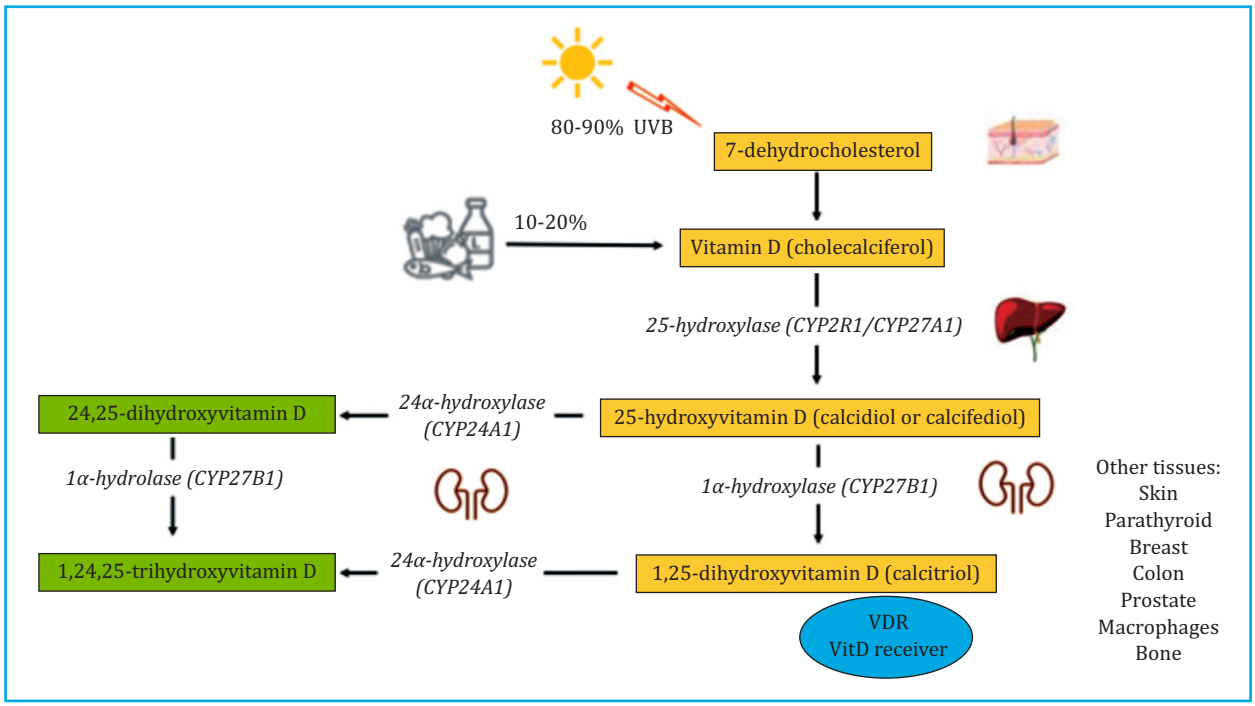
VDES modulates the expression of more than 3% of all the genes in the body, thus regulating different physiological processes in other organs and systems, such as muscle, the innate and adaptive immune system, the cardiovascular system or the pancreas, and regulates cell growth and hormone secretion throughout the body (Figure 2).

Thus, we now know that the functional deficiency of the VDES is associated not only with rickets, osteomalacia and osteoporosis, but also with an increased risk of suffering from cardiovascular, immunological, dermatological, metabolic diseases, depression, infections, infertility both male and female, pre-eclampsia and other effects on fetal development in pregnant women, and even cancer[8-16]. In this sense, in the last year it has been suggested that supplementation with cholecalciferol or calcifediol could have a beneficial effect in patients with COVID-19, an aspect that is extensively discussed in the SEIOMM position paper on COVID-19 and vitamin D[17].

Measurement of the total circulating 25-hydroxyvitamin D concentration constitutes a robust and reliable biomarker of the nutritional status of VDES. It is used by health authorities and Scientific Societies in Europe and America to establish the status of normality, which today continues to be the subject of debate.

Despite the high prevalence of "vitamin D" deficiency, even in developed countries, with high solar radiation or with easy access to supplementation, as is the case in Spain[18-20], there is no universal consensus to establish recommendations in the prevention and treatment of it.

Figure 1. Synthesis and metabolism of vitamin D



Our aim then is to update the position paper on the needs and optimal levels of 25-hydroxyvitamin D developed by the SEIOMM in 2011[21], based on the scientific evidence accumulated in recent years, and develop a series of recommendations agreed upon by experts from different disciplines on the prevention and treatment of vitamin D deficiency, focusing solely on musculoskeletal health.

2. Methodology

These recommendations have been developed in different stages, as defined below:

1) **Clinical question:** A multidisciplinary working group, composed of 10 physicians and researchers with experience in the management of vitamin D deficiency, formulated the relevant clinical questions regarding the aspects related to vitamin D treated in this document.

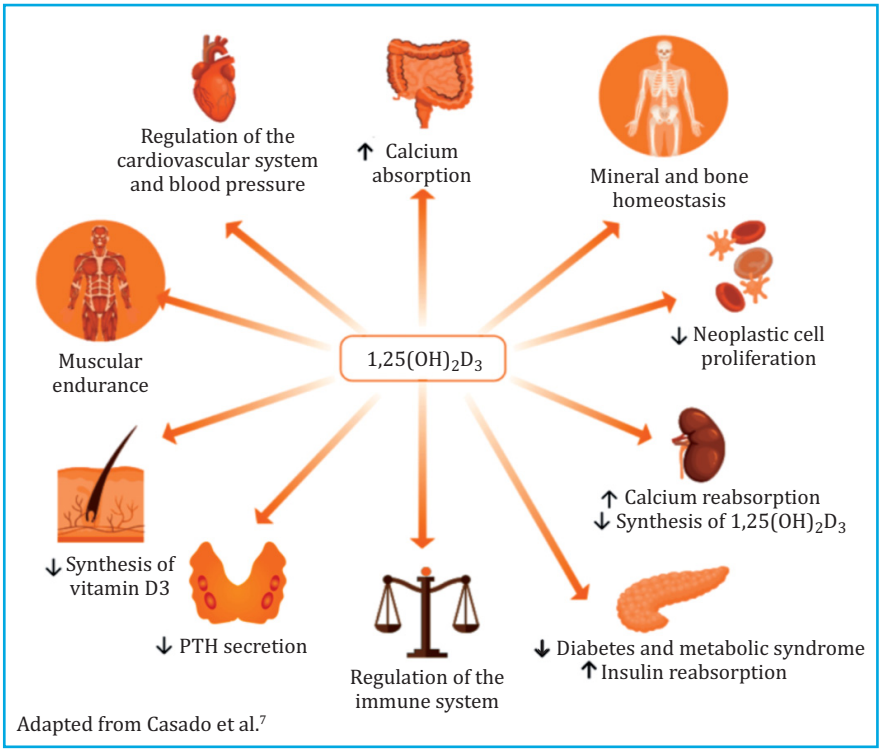
2) **Systematic literature review:** An independent team, made up of 1 doctor and 1 researcher, carried out a systematic review of the literature on studies related to the prevention and management of vitamin D deficiency. The search was carried out by consulting international databases. MEDLINE (via PubMed), EMBASE and Cochrane (Supplementary Table 1). Meta-analysis, systematic reviews, randomized controlled trials and observational studies were selected, conducted in humans and published in English or Spanish between July 15, 2016 and December 31, 2020. In addition, the potentially relevant citations of the identified articles, as well as as suggested by the working group were included.

Studies with antiresorptive or bone-forming drugs where vitamin D was not the comparator and studies conducted in Africa or Asia (except Japan) were excluded.

3) **Formulation of recommendations:** The working group established the recommendations according to the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to establish the degree of evidence and the strength of the recommendations[22]. The quality of the evidence is classified as very low ⊕, low ⊕⊕, moderate ⊕⊕⊕, or high ⊕⊕⊕⊕. The recommendations are based on evidence, and other factors such as, for example, the risk-benefit balance or the estimation of the consumption of resources or costs. They differentiate between strong recommendations (expressed as "we recommend" and number 1) and weak recommendations (expressed as "we suggest" and number 2), either in favor or against. All the recommendations were debated and agreed unanimously.

4) Finally, the working group prepared a draft of this document that was distributed to all SEIOMM associates for their **ratification**, having a period of 15 calendar days to make any allegation.

Figure 2. Main target tissues and actions of vitamin D



Adapted from Casado et al.[7]

3. Relationship between vitamin D and musculoskeletal health

25-hydroxyvitamin D deficiency and/or mutations in both the VDR and the activating enzyme (CYP27B1) cause alterations in muscle and bone[23]. The relationship between 25-hydroxyvitamin D deficiency and certain bone diseases such as osteomalacia and osteoporosis has long been well known[24].

3.1. Optimal 25-hydroxyvitamin D concentrations

Recommendation

- To attain the bone health benefits provided by vitamin D, it is recommended to maintain serum concentrations of 25-hydroxyvitamin D between 25 and 50 ng/mL (62.5-125 nmol/L) [1 ⊕⊕⊕◯].

- In patients with osteoporosis or at risk of fracture, it is suggested to maintain serum concentrations of 25-hydroxyvitamin D between 30 and 50 ng/mL [2 ⊕◯◯◯].

Evidence

There is some controversy about the levels of 25-hydroxyvitamin D necessary for optimal musculoskeletal health. In general, the minimum levels established in different clinical practice guidelines are between 20 and 30 ng/mL. For healthy populations, the European Food Safety Authority (EFSA) considers sufficient levels above 20 ng/mL, while the Spanish Society of Endocrinology and Nutrition (SEEN) considers that they should be above 30 ng/mL[25]. The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends levels above 20 ng/mL for postmenopausal women and above 30 ng/mL for frail elderly[26]. For its part, the Spanish Society of Rheumatology (SER) recommends maintaining 25-hydroxyvitamin D levels above 30 ng/mL for the population with osteoporosis[27].

An association between serum levels of 25-hydroxyvitamin D and bone mineral density (BMD) and muscle

strength has been described[28], and some studies suggest that levels of 25-hydroxyvitamin D equal to or greater than 24 ng/mL are associated with a reduction in the risk of falls[29] and fractures in the general population[30]. However, higher levels may be necessary to obtain other benefits beyond musculoskeletal health, taking into account that concentrations of 31 ng/mL are those that would be associated with a lower risk of mortality[31].

It has also been described that below 31 ng/mL of 25-hydroxyvitamin D, PTH levels begin to increase in certain populations[32] and the prevalence of secondary hyperparathyroidism is higher than 10%[33], a relevant aspect in patients with osteoporosis or at high risk of fracture.

In the general population, the panel considers it advisable to maintain serum levels of 25-hydroxyvitamin D above 25 ng/mL to ensure proper bone health. The analytical variability[34], the non-negligible proportion of patients with levels between 20 and 25 ng/mL who present secondary hyperparathyroidism and the increase in the intestinal absorption rate of calcium in some populations when going from 20 ng/ml to higher serum levels are reasons enough for this recommendation[35].

The recommended maximum serum level of 25-hydroxyvitamin D is also controversial, generally settling between 50 and 88 ng/mL[25,26,36]. A recent meta-analysis would support that the maximum concentrations should be in the low range, observing that the risk of mortality, although very slightly, tends to increase from 25-hydroxyvitamin D levels above 50 ng/mL[31]. In any case, it does not seem physiological to exceed 60 ng/mL, which are the maximum levels of 25-hydroxyvitamin D that are usually reached after intense sun exposure [37].

The panel considers that 25-hydroxyvitamin D values between 25 and 50 ng/mL would ensure a benefit in bone health while maintaining a good safety profile in the general population. However, and until there are more studies to corroborate these data, the panel suggests maintaining 25-hydroxyvitamin D levels between 30 and 50 ng/mL in patients with osteoporosis or at high risk of fracture.

It is not clear if the optimal values of 25-hydroxyvitamin D in the Caucasian population can be extrapolated to other types of races or ethnicities[38].

To minimize analytical variability, the panel considers it essential that the laboratory that performs the serum determination of 25-hydroxyvitamin D has the certification of a quality control program for the determinations, such as DEQAS[39] and the standardization of the determinations[40].

3.2. Screening for 25-hydroxyvitamin deficiency

Recommendation

Screening for 25-hydroxyvitamin deficiency is recommended in people with risk factors for hypovitaminosis D [1 ⊕⊕◯◯], and in people with muscle weakness and/or risk of falls [1 ⊕◯◯◯].

Evidence

Various risk factors (intrinsic and extrinsic) are related to 25-hydroxyvitamin deficiency (Table 1). Race is one of the most studied risk factors, observing that people with greater skin pigmentation have a greater risk of suffering from 25-hydroxyvitamin deficiency because UV radiation has less penetration[41]. Age is another classic risk factor due to changes in lifestyle habits (sedentary lifestyle, less sun exposure, less vitamin D synthesis capacity and less absorption capacity, etc.) and other physiological changes such as decreased blood pressure. hydroxylating capacity of vitamin D[42]. Obesity, especially related to the amount of abdominal fat, is another risk factor[43]. In addition, there are numerous risk factors that act synergistically. For this reason, screening for deficits is recommended in risk groups[25,31,41,44-49] (Table 1).

Recent studies have shown the correlation between 25-hydroxyvitamin D levels and muscle strength, mobility, and ultimately, the risk of fracture. An observational study carried out in 101 postmenopausal women suggested that low levels of 25-hydroxyvitamin D were significantly correlated with a decrease in muscle strength[44]. In a study carried out in a population over 70 years of age, it was observed how those men and women with 25-hydroxyvitamin D levels <20 ng/mL had poorer physical function and a slower gait speed than those with 25-hydroxyvitamin levels D ≥30 ng/mL ($p<0.01$)[50]. Loss of muscle strength/sarcopenia, along with other age-specific factors, could increase the risk of falls in people with bone loss, who are already at increased risk of fracture. In this sense, two recent meta-analysis carried out in more than 50,000 adults show that low levels of 25-hydroxyvitamin D are associated with significant increases in the risk of global fracture and hip fracture[30,51].

In addition, due to the risk of fracture in people with hypovitaminosis D, after a fall, screening is considered appropriate in subjects with muscle weakness and at risk of falls.

3.3. Vitamin D requirements

3.3.1. Feeding

Recommendations

- A daily intake (diet and/or supplements) of at least 600 IU of vitamin D_3 is suggested in children and adolescents[2 ⊕⊕◯◯].
- A daily intake (diet and/or supplements) of at least 800 IU of vitamin D_3 is suggested in the general adult population, and 800-1,000 IU in postmenopausal women and men over 50 years of age [2 ⊕⊕◯◯].
- A daily intake (diet and/or supplements) of 800-2,000 IU of vitamin D_3 is suggested in patients with osteoporosis, fractured patients and/or institutionalized elderly. [2 ⊕⊕◯◯].

Table 1. Risk factors and/or diseases associated with hypovitaminosis D

- Non-Caucasian race
- Old age and/or institutionalized people
- Restricted sun exposure
- Smoking
- Cognitive impairment
- Obesity (particularly abdominal)
- Malnutrition or risk of malnutrition
- Malabsorption syndrome or bariatric surgery
- Kidney or liver failure
- Hypo and hyperparathyroidism
- Rickets and/or osteomalacia
- Osteoporosis and/or fragility fractures
- Paget's disease of bone
- History of fracture
- Pregnancy and breastfeeding
- Use of drugs that interfere with cytochrome P450, such as:
  - Glucocorticoids
  - Antiepileptics
  - Antiretrovirals
  - Antifungals
  - Rifampicin

Table 2. Estimated vitamin D content according to food

	Vitamin D per 100 gr
Milk and derivatives	
Cheese	0.17 - 1.2 µg (6.8 - 48 UI)
Yoghurt	0.2- 1 µg (8 - 40 UI)
Whole milk	0.3 µg (12 UI)
Skimmed milk	0.1 µg (4 UI)
Milk curd	0.21 µg (8.4 UI)
Eggs and derivatives	
Hens eggs	2 - 11.4 µg (80 - 456 UI)
Meat products and derivatives	
Lung (lamb-veal)	11 - 12 µg (440 - 480 UI)
Duck	1 µg (40 UI)
Boiled ham	0.7 - 0.9 µg (28 - 36 UI)
Chicken, rabbit	0.2 - 0.4 µg (8 - 16 UI)
Fish, mollusks, crustaceans and derivatives	
Elver (raw)	110 µg (4,400 UI)
Salted herring	40 µg (1,600 UI)
Caviar	35 µg (1,400 UI)
Tuna, bonito, smoked herring and conge	3.5 - 34 µg (140 - 1,360 UI)
Smoked salmon and prawn	18-19 µg (720 - 760 UI)
Pomfret, horse mackerel, bream, and salema	14-16 µg (560 - 640 UI)
Anchovies (in vegetable oil)	11.8 µg (472 UI)
Sardine, salmon, perch, anchovies, swordfish, cod	7 - 8 µg (280 - 320 UI)
Oyster (raw)	3 µg (120 UI)
Fats and oils	
Cod liver oil	210 µg (8,400 UI)
Butter (low calorie)	12 µg (480 UI)
Margarine	2.5- 3.8 µg (100 - 152 UI)
Cereals and derivatives	
Cereals (wheat, rice, corn, muesli)	4 - 8 µg (160 - 320 UI)
Legumes, seeds, nuts and derivatives	
Almond milk	5 µg (200 UI)
Vegetables, vegetable derivatives	
Borage	13 µg (520 UI)

UI: international units BEDCA network[65]. https://www.bedca.net/bdpub/.

Evidence

Vitamin D requirements are those that ensure that 25-hydroxyvitamin D levels are maintained within the optimal range (25-50 ng/mL). The recommended intake of vitamin D has varied considerably over the past decades[21] and is still the subject of debate. In large part, the difference in existing criteria between different societies is due to the population to which they are directed: general population or patients with special needs[52,53].

The recommendations contained in this document are based on previous evidence, and especially on that published in recent years. To determine the amount of vitamin D that ensures optimal 25-hydroxyvitamin D values, we have compiled clinical trials and meta-analysis in which different cohorts (placebo versus vitamin D; or different doses of vitamin D) are compared by analyzing the levels of 25 -hydroxyvitamin D achieved. It is important to note the heterogeneity observed between the studies in relation to the results obtained, the levels considered adequate, and the baseline characteristics of the populations analyzed. Similarly, not in all the studies the vitamin D provided by the diet is strictly collected (Table 2), or adequate controls or adherence monitoring to the intervention are carried out, which makes the interpretation of the results difficult.

Until new studies supply more conclusive data, the panel is inclined to make conservative recommendations.

Premature infants: A recent study suggests that doses of 1,000 IU/day (diet plus supplement) of vitamin D achieve significantly higher values of 25-hydroxyvitamin D at 4 weeks than doses of 600 IU/day. However, at 8 weeks these differences would not be significant, and it is also observed that calcium levels reach a steady state at 4 weeks[54]. Given the lack of recommendations in preterm infants from the main guidelines, the panel considers a minimum intake of 600 IU/day advisable in premature infants.

Children and adolescents: The Institute of Medicine (IOM) recommends a dietary allowance of 400 IU/day in children under 1 year and 600 IU/day from 1 to 7 years[55]. In a recent meta-analysis that included a total of 5,403 children between the ages of 2 and 18, it was observed that age or sex would not affect vitamin D requirements[56]. In children under one year of age, no significant differences have been observed in the percentage of children

reaching values> 20 ng/mL between doses of 600 IU/day (supplement plus diet) and doses of 1,000 to 1,800 IU/day. These results would suggest that intakes of 600 IU/day would be as adequate to achieve optimal levels of 25-hydroxyvitamin D as higher doses. On the other hand, in a clinical trial carried out in Canadian children (2-8 years old) that compared the diet with dairy products fortified in vitamin D and without fortification (in a period of minimum UVB), the levels of 25-hydroxyvitamin D were higher than the 20 ng/mL in 85% of the subjects who consumed fortified dairy compared to 70% of the subjects in the control group[57].

Postmenopausal women: The daily intake of vitamin D recommended by the National Osteoporosis Foundation and the Institute of Medicine, for the prevention of hypovitaminosis D in women over 50 years of age is 800 to 1,000 IU/day[58,59]. In this sense, two randomized clinical trials[42,58] would suggest that intakes of 800 IU/day might not be sufficient, while doses of 1,000 IU/day would allow the majority of women (≥75%) to achieve 25-hydroxyvitamin D levels >20 ng/mL. For this reason, the panel recommends a daily intake (diet and/or supplements) of at least 800 IU of vitamin D in the general adult population (including pregnant or lactating women), and 800-1,000 IU in postmenopausal women. and men over 50 years of age.

Patients with osteoporosis or at high risk of vitamin D deficiency: The vitamin D requirements necessary for the population at risk of deficiency could vary considerably taking into account the special needs of each population. A randomized clinical trial carried out in 297 postmenopausal women with osteopenia or osteoporosis, suggests that supplementation with 800 IU/day (regardless of the contribution by diet), could be sufficient to maintain or moderately increase (~7 ng/mL) the 25-hydroxyvitamin D levels[60]. It should be noted that in this study, conducted in Norway, women ingested more than 8 µ/day (320 IU/day) of vitamin D in their diet and had baseline 25-hydroxyvitamin D levels >30 ng/ml, so these results cannot be extrapolated to other populations. Another study carried out in fractured elderly suggests that 85% would reach 25-hydroxyvitamin D levels above 20 ng/mL at 4 weeks with doses of 800 IU/day[61]. In the case of institutionalized elderly, a recent study suggests that 2,000 IU/daily of vitamin D are necessary to achieve optimal levels of 25-hydroxyvitamin D in plasma in the long term[62], while other studies suggest that lower daily intakes (1,000 IU/day) might be enough[63,64].

3.3.2. Sun exposure

Recommendation

- A 15-minute daily sun exposure on the face and arms is recommended in the Caucasian population between the months of March and October, with a protection factor between 15 and 30, depending on the latitude and intensity of the radiation. In the elderly population and in patients with osteoporosis, the recommended daily sun exposure would be 30 minutes [1 ⊕⊕◯◯].

Evidence

It is difficult to ascertain exactly the amount of vitamin D produced with sun exposure since it depends on factors such as age, skin phototype, season, time of day or geographical latitude[66].

Several studies have addressed this issue, such as one carried out in Japan that indicates that, in the afternoon hours during the summer months, 3.5 minutes of sun exposure would produce 5.5 µg of vitamin D3 (approximately 220 IU). However, in the winter months it could take between 22 minutes and 271 minutes depending on the time and weather conditions[67]. Other authors suggest that exposing 20% of the body surface to a minimum erythema dose of 0.5 would be equivalent to ingesting 1,400-2,000 IU of vitamin D[68]. Finally, in a recent meta-analysis, a mathematical formula has been postulated that would allow determining the increase in 25-hydroxyvitamin D based on the radiation received, the basal level of 25-hydroxyvitamin D and the area of the body exposed[69]. According to this formula, on a day with a moderate radiation index, a 12-minute sun exposure on the face and hands would be sufficient to increase the 25-hydroxyvitamin D level by 6.3 ng/mL. However, it does not take into account the differences that exist according to skin type.

The Australian Society for Endocrinology and Osteoporosis establishes specific recommendations such as sunbathing for 6 to 40 minutes a day on the face and arms depending on latitude, time of day, season and skin type[70].

However, the increased risk of developing melanoma due to excessive sun exposure has meant that dermatological societies such as the American Academy of Dermatology recommend that the source of vitamin D be through nutrition and not by sun exposure (outdoors or in UVB cabinets)[71]. The European Academy of Dermatology and Venereology notes the risk of using sun booths to ensure adequate 25-hydroxyvitamin D levels, but does not specifically restrict limited sun exposure[72,73]. Other societies, however, do state that adequate sun exposure is an appropriate source of vitamin D. Thus, the Spanish Society of Dermatology and Venereology considers it healthy to combine limited sun exposure and adequate nutrition.

A group of experts, based on a review of the literature, showed that the use of sun creams, even with a high protection factor (30 or more), does not interfere with the skin synthesis of vitamin[74].

To maintain skin synthesis of vitamin D, the panel recommends a 15-minute daily sun exposure on the face and arms in the Caucasian population during the months of March and October. In the elderly population and patients with osteoporosis, the panel recommends a daily sun exposure, between the months of March and October, of about 30 minutes, provided there are no contraindications, and also advising the use of a protection factor between 15 and 30, depending on latitude and intensity of UVB radiation[74].

3.4. Vitamin D supplementation

3.4.1. General recommendations

Recommendation

- It is recommended to use cholecalciferol or calcifediol to supplement or treat patients with 25-hydroxyvitamin D deficiency, reserving calcitriol and alfacalcidol for populations with special diseases [1 ⊕⊕◯◯].

- It is suggested to assess the dose and type of metabolite required based on the baseline levels of 25-hydroxyvitamin D, associated pathology and characteristics of the individual [2 ⊕◯◯◯].

- It is recommended long-term supplementation in the population at risk of 25-hydroxyvitamin D deficiency (<25 ng/mL) [1 ⊕⊕◯◯].

- Low-dose vitamin D supplementation is recommended, except when rapid normalization of 25-hydroxyvitamin D concentrations is necessary [1 ⊕⊕◯◯].

- Monitoring serum concentrations of 25-hydroxyvitamin D is suggested to assess the response to supplementation every 3-4 months until adequate concentrations are reached, and then every 6 or 12 months [2 ⊕◯◯◯].

- In patients treated with calcifediol at a dose of 266 µg, it is suggested that 25-hydroxyvitamin D levels not be determined until at least 7 days after the last intake [2 ⊕◯◯◯].

- In patients with insufficient response after supplementation, it is suggested to increase the frequency or dose, or to consider a change in the type of supplement/treatment [2◯◯◯◯].

- For good bone health, it is recommended to accompany supplementation or treatment with an adequate intake of calcium (1,000-1,200 mg/day preferably from food), and moderate intensity physical exercise, especially in patients with osteoporosis or at risk of suffering falls or fractures [1⊕⊕⊕◯].

Evidence

Effect of vitamin D on musculoskeletal health

The results on the effect of vitamin D supplementation identified in the literature are heterogeneous due to the difference between the studied populations (postmenopause, osteoporosis, the elderly or the general population), the evaluated strategies (combination or not with calcium and/or exercise), and the outcome variables analyzed (strength, mobility, stability, falls, fractures and/or BMD).

In relation to strength, a meta-analysis performed in postmenopausal women[75] and a randomized trial in institutionalized elderly[63] suggest that vitamin D supplementation and exercise increase muscle strength. However, in 4 other studies conducted in the elderly, no significant increase in strength was observed without exercise[61,76,77] or in combination with exercise[78]. Regarding mobility, in 3 studies conducted in the elderly receiving vitamin D supplements[61] in combination with exercise[63,78], a significant increase was observed. On the contrary, a meta-analysis suggests that vitamin D supplementation could even cause a slight (albeit significant) decrease in mobility in institutionalized elderly[76]. As for stability, a recent study suggests that supplementation with vitamin D improves stability in postmenopausal women[79]. For its part, a meta-analysis carried out in the general adult population found a marginally significant improvement in BMD in the population treated with vitamin D compared to the untreated population[80].

One of the purposes of vitamin D supplementation is to reduce falls, and ultimately fractures. In this sense, 2 meta-analysis and 3 randomized trials carried out in the elderly and postmenopausal women suggest that vitamin D supplementation reduces the risk of falls. However, in the general population this benefit would not be demonstrated[80,81]. Interestingly, although various previous meta-analysis had found a correlation between calcium and vitamin D supplementation and a reduction in the risk of fracture[82,83], subsequent studies identified in the present review would not corroborate a statistically significant risk reduction[61,80,84].

The effect of vitamin D supplementation depends on the baseline values of 25-hydroxyvitamin D, and it has been shown that supplementation causes a better response the greater the deficiency[85]. In this sense, it is important to note that in many studies the effect of vitamin D supplementation is evaluated, including people who do not have 25-hydroxyvitamin D deficiency, and who, therefore, would not need to be supplemented. Specifically, in the review carried out for this document, only 8% of the studies identified had 25-hydroxyvitamin D levels lower than 20 or 30 ng/mL as inclusion criteria. In fact, combined analysis support that vitamin D supplements only prevent fractures and falls in people with 25-hydroxyvitamin D deficiency[80]. Therefore, in line with what has been argued by many authors[13,86-88], we consider that it cannot be concluded that vitamin D supplementation is not effective in people with hypovitaminosis, in terms of reducing fractures or falls.

Vitamin D derivates

Currently, for the treatment of 25-hydroxyvitamin D deficiency there are different metabolites of the SEVD marketed in Spain: cholecalciferol and calcifediol for deficiency diseases, in addition to calcitriol and alfacalcidol for populations with special conditions, such as chronic kidney disease, rickets/osteomalacia hypophosphatemic linked to the X chromosome, hypophosphatemic autosomal and oncogenic among others.

Available vitamin D metabolites have different half-life, potency and speed of action. Thus, calcifediol has a shorter half-life, is 3-6 times more potent, and has a faster action than cholecalciferol in the treatment of vitamin D deficiency[89].

In general, both cholecalciferol and calcifediol are effective and safe forms for the prevention and treatment of vitamin D deficiency in all populations. However, in some specific situations one metabolite may be preferable over the other.

In patients with chronic liver disease, treatment with drugs that compete with the synthesis of 25-hydroxyvitamin D or that are severely deficient and require rapid replacement, treatment with calcifediol may be preferable.

In patients with primary hyperparathyroidism or in those in whom 25-hydroxyvitamin D levels cannot be monitored, supplementation with cholecalciferol may be preferable[90].

The dose, frequency, and duration of supplementation/treatment are factors that are independently associated with 25-hydroxyvitamin D levels[91]. The dose and frequency will depend on the severity of the deficit, its causes and the formulation of the metabolite used. In general, for vitamin D it has been observed that different dosing regimens have similar results[92]. On the other hand, various studies comparing cohorts treated with different doses suggest that in the medium term, moderate doses would have a similar effect to that of higher doses[54,57,62,93], even too high doses (mega doses) could increase the risk of falls, fractures, and even lower BMD[94-96].

However, it is important to mention that certain groups of patients may require higher doses and/or administered parenterally, such as, for example, malabsorptive symptoms, morbid obesity or undergoing bariatric surgery. Therefore, we recommend calculating the dose in each case, generally opting for low doses, and increasing it or changing the supplement in the event of an inadequate response.

There is no single supplementation regimen in patients with 25-hydroxyvitamin D deficiency. Table 4 shows the regimen recommended by the panel for both the general population and for patients with osteoporosis or other populations at risk of 25-hydroxyvitamin D deficiency, whether opting for cholecalciferol or calcifediol.

Follow-up monitoring

Another key point is the follow-up of patients with 25-hydroxyvitamin D deficiency or insufficiency. It is estimated that plasma levels of 25-hydroxyvitamin D stabilize after 2 or 3 months of starting supplementation[56,61,62, 78.97].

In line with the Endocrine Society[55] and SEEN[25], we recommend monitoring patients initially every 3-4 months, and once the appropriate concentrations are reached, every 6-12 months.

In a pharmacokinetic study, the administration of a single 140 µg dose of calcifediol produced an initial peak in the plasma concentration of 25-hydroxyvitamin D, which normalize after 7 days. However, this same dose of cholecalciferol achieved progressive increases in 25-hydroxyvitamin D levels, which did not reach the maximum peak until after 3 months[98]. For this reason, in patients treated with calcifediol, the determination of 25-hydroxyvitamin D should preferably be performed at least 7 days after the last administration, while with the supplementation with cholecalciferol, the time of determination does not matter.

Calcium intake

For a suitable effect of the anti-osteoporotic drugs, it is advisable, it is advisable to ensure an optimal daily intake of calcium (approximately between 1 and 1.2 grams), being preferable to do so through food whenever possible[25,59,82,99-102].

3.5. Prevention of 25-hydroxyvitamin D deficiency and maintenance

Recommendation

- In the general population, optimal sun exposure and adequate nutrition are recommended, and if this is not enough, it should be supplemented with 800 IU/day (20 µg/day) of cholecalciferol (or 25,000 IU/month; 625 µg/month) [1 ⊕⊕⊕◯].

- In patients with osteoporosis or a population at risk of vitamin D deficiency, supplementation with cholecalciferol at doses of 1,000-2,000 IU/day (25-50 µg/day) or calcifediol at doses of 8-12 µg/day (480 -720 IU/day). If a regimen with a lower frequency of administration is preferred, the administration of 25,000-30.000 IU of cholecalciferol/15 days (50,000-60,000 IU/month) or 266 µg of calcifediol every 3-4 weeks is recommended [1 ⊕⊕⊕◯].

- Obese patients, with malabsorption syndromes, bariatric surgery or treated with drugs that affect the metabolism of vitamin D (eg antiepileptics, glucocorticoids, rifampicin or antiretrovirals) may require doses 2-3 times higher than usual (3,000-6,000 IU/day of cholecalciferol), being preferable the administration of calcifediol (up to 12 µg/day or more) or, in cases of severe malabsorption, as in some cases of bariatric surgery "bypass type", the administration of parenteral vitamin D could be needed [1 ⊕⊕◯◯].

Evidence

As previously mentioned, and based on the vitamin D requirements in each population, the panel recommends a daily intake (diet and/or supplements) of at least 800 IU (20 µg/day) of vitamin D in the general population. Adult, and 800-1,000 IU (20-25 µg/day) in postmenopausal women and men over 50 years.

In studies carried out in the elderly and institutionalized population in which an improvement in musculoskeletal health is observed with vitamin D supplementation (alone or in combination with calcium and exercise), this improvement is achieved with doses greater than 700 IU/day[29], and generally between 800 and 1,000 IU/day[61,63,64,78].

In patients with osteoporosis, especially if they receive powerful antiresorptive treatments, it is necessary to ensure an adequate supply of calcium and vitamin D. In this way, the risk of hypocalcemia is minimized, and a better therapeutic response is ensured[103,104].

As we have discussed previously, the association between 25-hydroxyvitamin D deficiency and obesity is well established, although its causes are still under study[105]. Although obesity has traditionally been considered a protective factor against fragility fractures and some studies suggest this[106], others question the cause-effect relationship[107-109]. Obese individuals are estimated to require higher doses of vitamin D (2 to 3 times higher) than the non-obese population[110]. Likewise, in cases of severe malabsorption, such as "bypass-type" bariatric surgery, parenteral administration may be needed[111].

Various medications (such as antiepileptic agents, glucocorticoids, rifampin, or antiretroviral drugs) can interfere with vitamin D and bone metabolism by various mechanisms, such as modifying 24-hydroxylase activity[112].

In the same way, in patients treated with drugs that can affect the metabolism of vitamin D, higher doses are recommended. Thus, for example, the sustained use of glucocorticoids induces bone loss by reducing intestinal calcium absorption and increasing renal excretion, suggesting minimum doses of 1,800 IU/day for this type of patients[113]. In the same way that glucocorticoid therapy is associated with bone loss, chronic antiretroviral therapies are associated with a decrease in BMD in HIV-infected people[114]. The European AIDS Clinical Society recommends the administration of between 800 and 2,000 IU/day in HIV patients to achieve 25-hydroxyvitamin D levels above 20 ng/mL[115]. Likewise, it has been observed that antiepileptic therapies are associated with a decrease in the levels of 25-hydroxyvitamin D[49,116], which could be prevented, at least in part, with high doses of vitamin D (equivalent to 2,000 IU/day)[117].

Bariatric surgery also causes a reduction in BMD, the deterioration of bone structure and an increase in bone resorption, due to the malabsorptive process triggered by the surgery, increasing the risk of fragility fracture[118-120]. Bariatric surgery patients receiving cholecalciferol before surgery (28,000 IU...) (28,000 IU/week for 8 weeks) and after surgery (16,000 IU/week), along with calcium and exercise, experience significantly less decline in bone health[121]. However, more studies are necessary to determine the effect and the necessary doses in these patients. In any case, some guidelines such as the American Association of Clinical Endocrinologists, The Obesity Society, and the American Society for Metabolic & Bariatric Surgery, have recommended supplementation with high doses of vitamin D (3,000 to 7,000 IU/day) for several years. in these patients, and in some cases parenteral administration may be necessary[122,123]. In these cases, it must be requested as a foreign medication as it is not available in Spain.

Calcifediol, due to its pharmacokinetic characteristics, may be preferable in patients with interference in the synthesis of 25-hydroxyvitamin D (eg treatment with anti-epileptic drugs), with a lower bio-availability of vitamin D3 (eg obesity) or with severe malabsorption (eg bariatric surgery)[124].

4. Conclusions

This document includes a set of recommendations for the prevention and treatment of 25-hydroxyvitamin D deficiency prepared by a multidisciplinary group of experts, based on the most recent scientific evidence, and ratified by the SEIOMM.

Table 3. Recommended supplementation regimen with cholecalciferol or calcifediol in patients with 25-hydroxyvitamin D deficiency

Population (desirable levels of 25-hydroxyvitamin D)	Serum 25-hydroxyvitamin D levels	Treatment (any of the suggested regimens)
General population (>25 ng/mL)	<10 ng/mL (severe deficiency)	Calcifediol: 266 µg/week *(16,000 IU/week *)* for 5 weeks . Cholecalciferol: 50,000 IU/week for 4-6 weeks. Then continue with the insufficiency regimen.
	10-25 ng/mL (insufficiency)	Colecalciferol: 25.000 UI/month or 800 UI/day. Calcifediol: 266 µg/month *(16.000 UI/month*)*.
Osteoporosis and other population groups at risk of vitamin D deficiency (>30 ng/mL)	<10 ng/mL (severe deficiency)	Calcifediol 266 µg/week *(16.000 UI/week*)* for 5 weeks. Colecalciferol: 50.000 UI/week for 6-8 weeks. Then continue with the insufficiency regimen.
	10-30 ng/mL (insufficiency)	Colecalciferol: 50.000 UI/month or 1.000-2.000 UI/day. Calcifediol: 266 µg/3-4 weeks *(16.000 UI/3-4 weeks*).*

*: equivalence according to technical data sheet. Actually, this equivalence cannot be established, and it is preferable to use µg for the doses of calcifediol.

These recommendations are an update of those made in the SEIOMM Position Paper on Optimal 25-Hydroxyvitamin D Needs and Levels. The optimal 25-hydroxyvitamin D levels currently recommended are slightly lower (25-50 ng/mL) than those recommended in 2011 (30-75 ng/mL), while the 25-hydroxyvitamin D levels required by different populations as patients with osteoporosis (30-50 ng/mL), they would be, in general, similar to those previously recommended, including premature infants. In addition, it delves into aspects such as, for example, sun exposure, the populations in which it is necessary to supplement with vitamin D or treat, with what dose to do it, and the frequency of patient monitoring.

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Supplemental Table 1. Search terms: vitamin D and musculoskeletal health

VITAMIN D
Vitamin D [MeSH]
Vitamin D Deficiency [MeSH]
"hypovitaminosis D" [ti]
250HD [tiab]
"Vitamin D*" [tiab]
Cholecalciferol [MeSH]
Cholecalciferol [tiab]
Calcifediol [tiab]
Ergocalciferols [MeSH]
Ergocalciferol [tiab]
QUESTION 1: WHAT ARE THE ADEQUATE VALUES OF VITAMIN D?
"Level" [tiab]
"Concentration" [tiab]
QUESTION 2: WHAT TYPE OF PATIENT SHOULD BE SCREENED FOR POSSIBLE HYPOVITAMINOSIS?
Diagnosis [MeSH]
"Diagnostic Screening Programs" [MeSH]
Screening [ti]
"Population-based screening" [tiab]
"Risk Factors" [MeSH]
"Risk factors" [ti]
QUESTION 3: WHAT ARE THE REQUIREMENTS FOR VITAMIN D?
"Diet, Food, and Nutrition" [MeSH]
"Nutritional requirement" [tiab]
QUESTION 4: WHAT ARE THE SOURCES OF VITAMIN D?
Sunlight [MesH]
"light exposure" [ti]
Daylight [ti]
"source" [ti]
"nutrition*" [ti]
"food" [ti]

Supplemental Table 1. Search terms: vitamin D and musculoskeletal health (cont.)

QUESTION 5: WHICH PATIENTS CAN BENEFIT FROM VITAMIN D SUPPLEMENTATION? WHAT IS THE RECOMMENDED TYPE OF VITAMIN, DOSE AND DURATION OF TREATMENT? ALONE OR WITH CALCIUM?
Outcome Assessment (Health Care) [MeSH]
"Dose-Response Relationship, Drug" [MeSH]
Dose [ti]
"therapeutic use" [MeSH]
Effectiveness [ti]
Supplement [ti]
QUESTION 6: WHAT IS THE APPROPRIATE MONITORING FREQUENCY?
"Drug Monitoring" [MeSH]
"monitoring" [ti]
"Continuity of Patient Care" [MeSH]
SALUD ÓSEA
"Bone Density" [MeSH]
"Osteoporosis" [MeSH]
"Osteoporosis" [ti]
Bone Demineralization, Pathologic [MeSH]
"Fracture, bone" [MeSH]
Fracture [ti]
"Accidental falls" [MeSH]
Falls [ti]
"Muscle Strength" [MeSH]
"Muscle Strength" [ti]
{OR #1-#10} AND {OR #11-#35} AND {OR #36-#45}

("Vitamin D" [MeSH] OR "Vitamin D Deficiency" [MeSH] OR "hypovitaminosis D" [ti] OR "Vitamin D*" [tiab] OR "250HD" [tiab] OR "Cholecalciferol" [MeSH] OR "Cholecalciferol" [tiab] OR "Calcifediol" [tiab] OR "Ergocalciferols" [MeSH] OR "Ergocalciferol" [tiab]) AND ("Level" [tiab] OR "Concentration" [tiab] OR "Diagnosis" [MeSH] OR "Diagnostic Screening Programs" [MeSH] OR "Screening" [ti] OR "Population-based screening" [tiab] OR "Risk Factors" [MeSH] OR "Risk factors" [ti] OR "Diet, Food, and Nutrition" [MeSH] OR "Nutritional requirement" [tiab] OR "Sunlight" [MesH] OR "light exposure" [ti] OR "Daylight" [ti] OR "source" [ti] OR "nutrition*" [ti] OR "food" [ti] OR "Outcome Assessment (Health Care)" [MeSH] OR "Dose-Response Relationship, Drug" [MeSH] OR "Dose" [ti] OR "therapeutic use" [MeSH] OR "Effectiveness" [ti] OR "supplement" [ti] OR "Drug Monitoring" [MeSH] OR "monitoring" [ti] OR "Continuity of Patient Care" [MeSH]) AND ("Bone Density" [MeSH] OR "Osteoporosis" [MeSH] OR "Osteoporosis" [ti] OR "Bone Demineralization, Pathologic" [MeSH] OR "Fracture, bone" [MeSH] OR "Fracture" [ti] OR "Accidental falls" [MeSH] OR "Falls" [ti] OR "Muscle Strength" [MeSH] OR "Muscle Strength" [ti]).

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Maxillary metastasis due to pulmonary myofibroblastic tumor detected in study [18-F] FDG PET/CT

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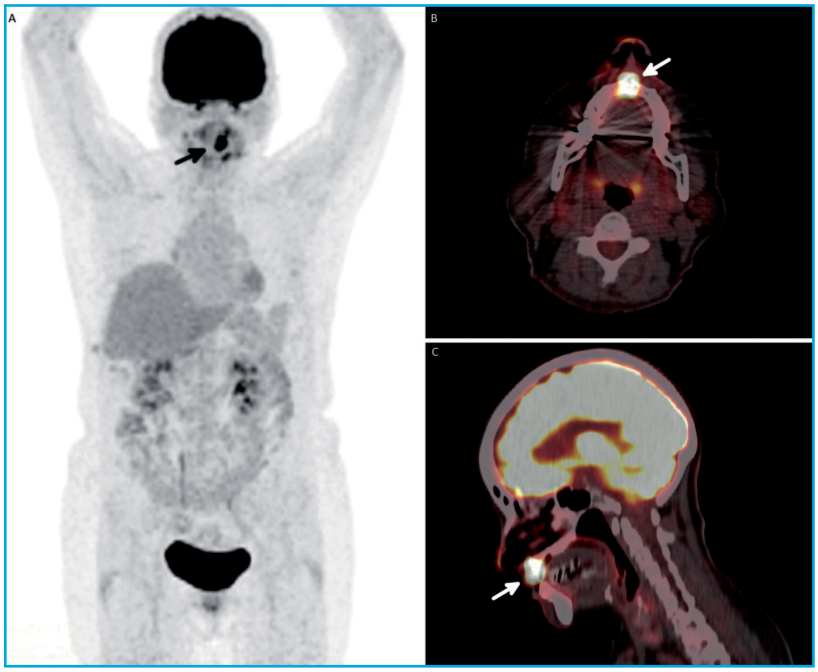
We present the case of a 62-year-old woman with a history of a fibrohistiocytic variant of a pulmonary inflammatory myofibroblastic tumor treated by a lobectomy of the right lower lobe and lymphadenectomy of the intrapulmonary area and pulmonary ligament, and a history of tooth extraction 11 due to a vestibular fistula torpid.

In a control [18-F] FDG PET/CT study, a solitary hypermetabolic lesion suggestive of malignancy was observed in the gingival area of the upper jaw (Figure1 A-C) and 3D reconstruction (Figure 2).

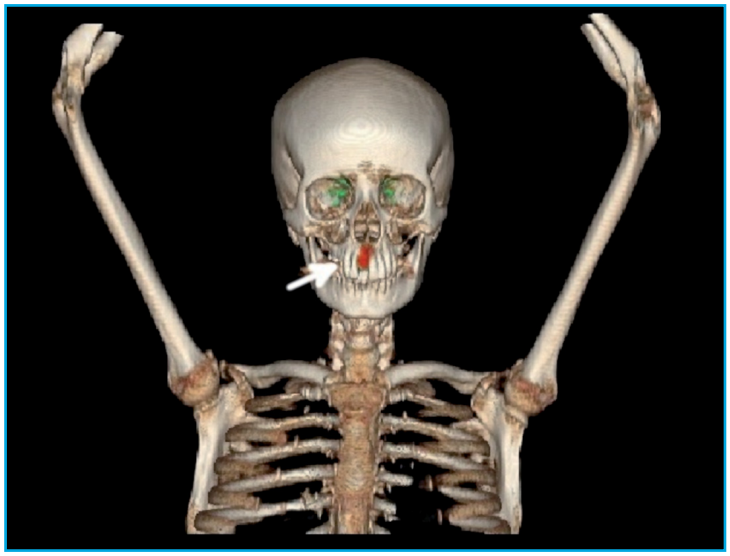
Given the suspicion of malignancy, a partial maxillectomy of teeth 13-23 was carried out with placement of an obturator prosthesis. Analysis confirmed the metastatic etiology by observing hypercellular areas with a fasciculate pattern and broader sarcomatoid areas. Immunohistochemical analysis showed strong ALK expression, higher FLI1 expression, and lower CD10 and TLE1 expression. At present, the patient remains asymptomatic.

Figure 1. Study [18-F] FDG PET/CT in which a solitary hypermetabolic lesion is observed in the gingival area of the upper jaw (SUVmax 27), which corresponds in the morphological image to an exophytic lesion located on the extraction of the tooth 11 in the maximum intensity projection (MIP). (Figure 1A, arrow), axial section (Figure 1B, arrow) and sagittal section (Figure 1C, arrow)



Inflammatory myofibroblastic tumor (IMT), also known as inflammatory pseudotumor, xanthoma, plasma cell granuloma, pseudosarcoma, lymphoid hematoma, myxoid hamartoma and inflammatory myofibrohistiocytic proliferation[1,2], is an uncommon neoplastic growth of mesenchymal proliferation and myofibroblast line at the expense of myofibroblasts. an obvious inflammatory infiltrate composed of plasma cells, lymphocytes, and eosinophils[1-4]. This has generally been considered a benign tumor. At present, it is considered a neoplasm of intermediate malignancy, however, as it has a tendency to local aggressiveness and recurrences and, on rare occasions, may trigger distant metastases[1-4]. The etiology is unknown at this point in time, although inflammation, autoimmunity and previous infections are suggested as possible causes[1-4]. IMT may be found in a wide variety of locations, the most common being the pulmonary location, followed by the abdominal, skin, soft tissue, genital, and mediastinum. It is typical of pediatric age and young adults[2].

Figure 2. 3D reconstruction of study [18F] FDG PET/CT that identified a hyper-metabolic lesion on an exophytic lesion located on the extraction of tooth 11 (arrow)



Normally, IMT presents asymptomatically, being detected as an incidental finding in a radiological test, although it can occasionally produce symptoms secondary to mass effect and nonspecific symptoms such as weight loss, anemia or fever secondary to the production of cytokines (mainly IL-1)[3]. It is necessary to perform a differential diagnosis against other non-neoplastic entities such as reparative, autoimmune or postinfection processes[2,4].

The [18-F] FDG PET/CT study is a very useful diagnostic test in the evaluation of the cancer patient. [18-F] FDG is a glucose analog that accumulates in body cells in proportion to glucose utilization. The accumulation of [18-F] FDG in most tumor cells by over-expression of the GLUT-1 transporter is characteristic, although active inflammatory processes can also present a physiological increase in [18F] FDG in granulocytes and mononuclear cells. IMT can show a heterogeneous uptake of [18F] FDG that can be explained by the variability of cellularity, the rate of cell proliferation and nuclear atypia of tumor cells, as well as the composition, proportion and activation of inflammatory cells[1,3,4.] The treatment of choice is complete surgical resection, being curative in 90% of cases. It has been shown that previous steroidal or non-steroidal anti-inflammatory treatment can be useful to reduce tumor size, in local recurrences or in unresectable tumors[1-4].

In conclusion, we present the detection by an [18-F] FDG PET/CT study of a metastasis in the head and neck region due to a tumor that rarely presents distant metastatic involvement.

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

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Multidisciplinary approach to diagnostic imaging in melorheostosis

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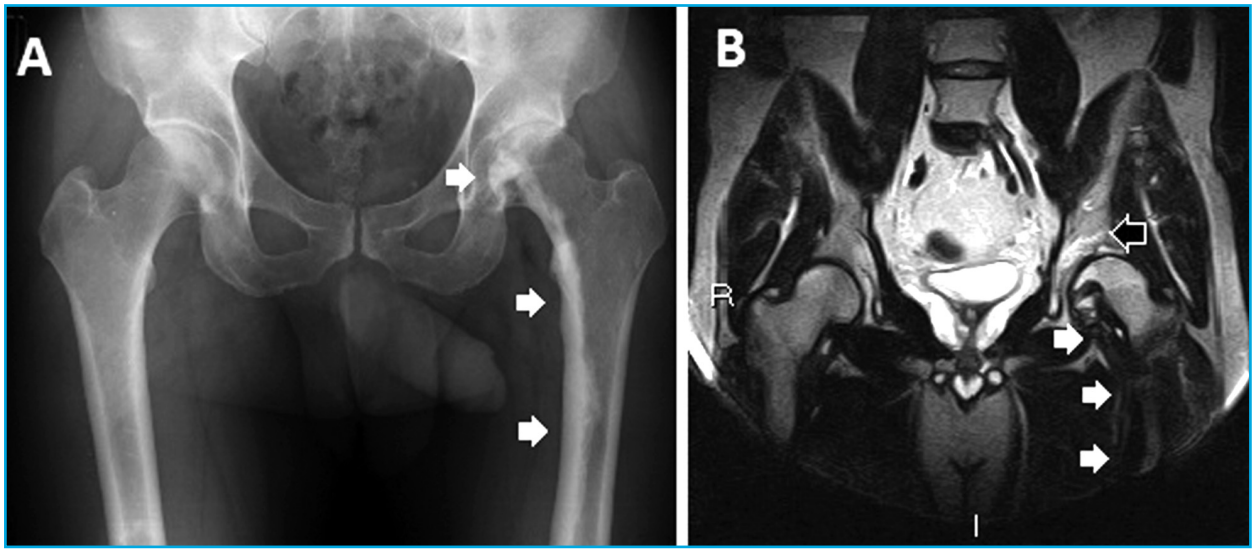
We present a 44-year-old man with a history of multiple trauma in childhood and trauma to the left hip eight months before the consultation, who consulted for pain of short duration (5 days) in the left hip, presenting limited range of movement on physical examination in the extreme degrees of the left hip, without signs of local infection or laboratory abnormalities. The x-ray of the hips (Figure 1A) showed periosteal hyperostosis along the inner cortex of the left femur (white arrows), giving rise to a characteristic image of "molten wax dripping down the side of a candle". (Figure 1B) Cortical thickening appeared as hypointense in all image sequences (white arrows), in addition to showing bone edema of the femoral head related to degenerative joint disease (black arrow). A bone gamma scan study was requested.

The early phases of the bone gamma scan study with 28 mCi (1036 MBq) of Tc99m-MDP (Figure 2) showed increased vascularity in the left hip (black arrows). The late full-body image highlighted the focal uptake of the radiotracer in the upper region of the femoroacetabular joint (black arrow), corresponding in the SPECT/CT fusion images with an area of sclerosis and degenerative joint disease. In addition, another deposit of less intensity was identified in the left femoral shaft (white arrows), in relation to the radiological thickening of the inner edge of the cortex seen in the fused images.

Melorrheostosis is a benign bone dysplasia that predominantly affects the appendicular skeleton and adjacent soft tissues[1]. The bone distribution is usually asymmetric[2] and can be monostotic or polyostotic. It is

Figure 1. Simple AP radiography of the hips (A) and T2 STIR sequence coronal plane MRI (B)



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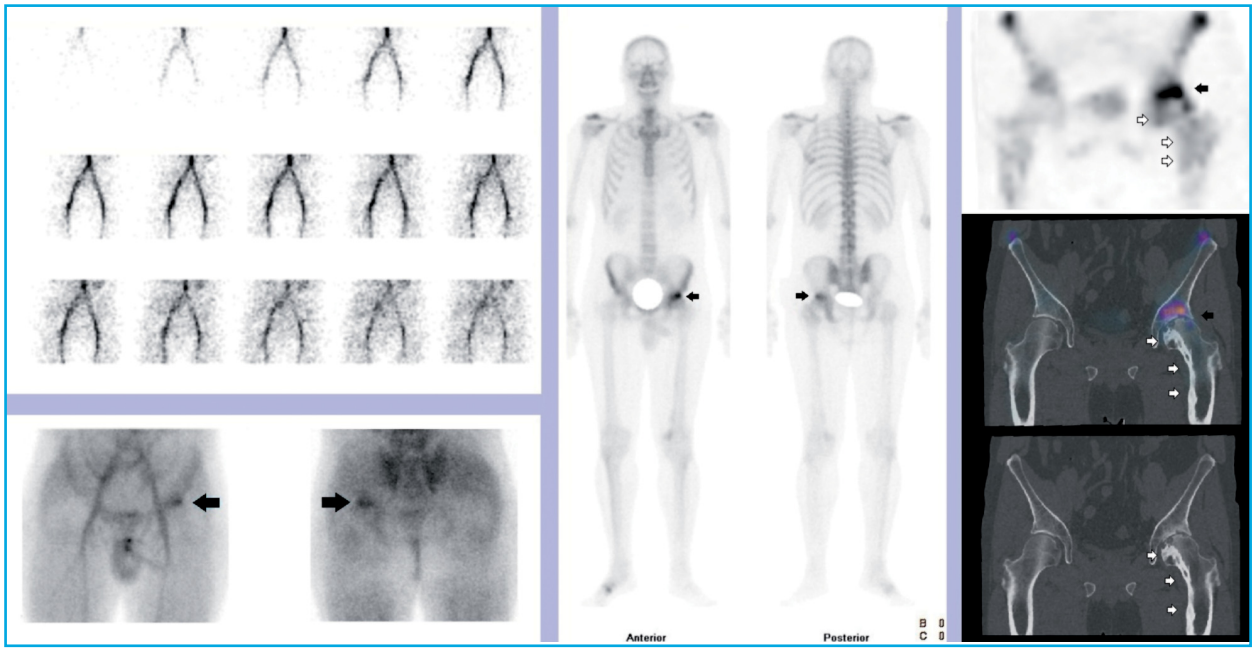
caused by an abnormality of embryonic development with a sclerotome distribution[3]. There is no standard treatment, so it must be planned individually. The efficacy of bisphosphonates on pain has been described[4,5], but in some cases corrective surgery for bone deformities and osteodegenerative sequelae may be necessary.

Diagnosis is often made by conventional radiography, by identifying cortical hyperostosis with a "candle wax" image[6,7]. Since laboratory tests are normal, the bone scan pattern is crucial for the differential diagnosis of other infiltrative diseases and other osteodysplastic syndromes[8,9].

Figure 2. 3-phase 99mTc-MDP bone scan of the hips, full-body scan, and SPECT/CT of the hips



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

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Regarding the position paper of the SEIOMM on COVID-19 and vitamin D

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To the editors,

We read with interest the position paper of the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM) on COVID-19 and vitamin D, recently published in your journal[1]. This document helps clarify the role of vitamin D in this infectious disease. One of its conclusions caught our attention. In the final section on the risk/benefit ratio of administering vitamin D, it stated that "it is considered that the administration of 10,000 IU/day of cholecalciferol or 4,000 IU/day of calcifediol is safe". This assertion is bibliographically referenced with a review on the benefit-risk balance of vitamin D by Bischoff-Ferrari et al.[2] In this paper, an evaluation of the effectiveness and safety of several clinical trials in which cholecalciferol (vitamin D3) [mostly] or ergocalciferol (vitamin D2). In no case does the review collect clinical data generated from calcifediol supplementation, so including calcifediol in the phrase seems to us to generate some confusion.

Actually, the authors' thesis of the cited article is that, based on the scientific evidence available at the date of publication, it could be concluded that 10,000 IU of cholecalciferol/day may be the maximum safety limit for supplementation with vitamin D (it is even said that there is no robust evidence that even higher doses cause severe hypercalcaemia and/or vascular calcifications) and that doses of up to 4,000 IU of cholecalciferol/day are safe, without mentioning anything about calcifediol as an alternative supplementation with vitamin D. We would like to show that we agree with the conclusions of Bischoff-Ferrari et al.[2] Therefore, we consider that the statement made in the SEIOMM document on vitamin D and COVID- 19 regarding the safety of vitamin D should refer only to cholecalciferol.

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Authors' response

We have read with interest the letter by Lopez-Medrano et al. regarding the SEIOMM Position Paper on COVID and vitamin D. They are correct when they indicate that the article by Bishoff-Ferrari et al.[1] assesses the effectiveness and safety of several clinical trials in which cholecalciferol (vitamin D3) [mostly] or ergocalciferol (vitamin D2) was used, the dose being 10,000 IU daily, the maximum safety limit for supplementation with vitamin D. The maximum dose of 25-hydroxyvitamin D that has been indicated is determined by the difference in potency between the two supplements, 2 to 4 times more potent than calcifediol[2] . The equivalence recently reported by Rizoli[3], 10 micrograms of calcifediol (600 IU)/day would equal 1,200 IU of cholecalciferol. The document presented is not a systematic review and has a limited number of citations, so a generic citation was preferred.

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