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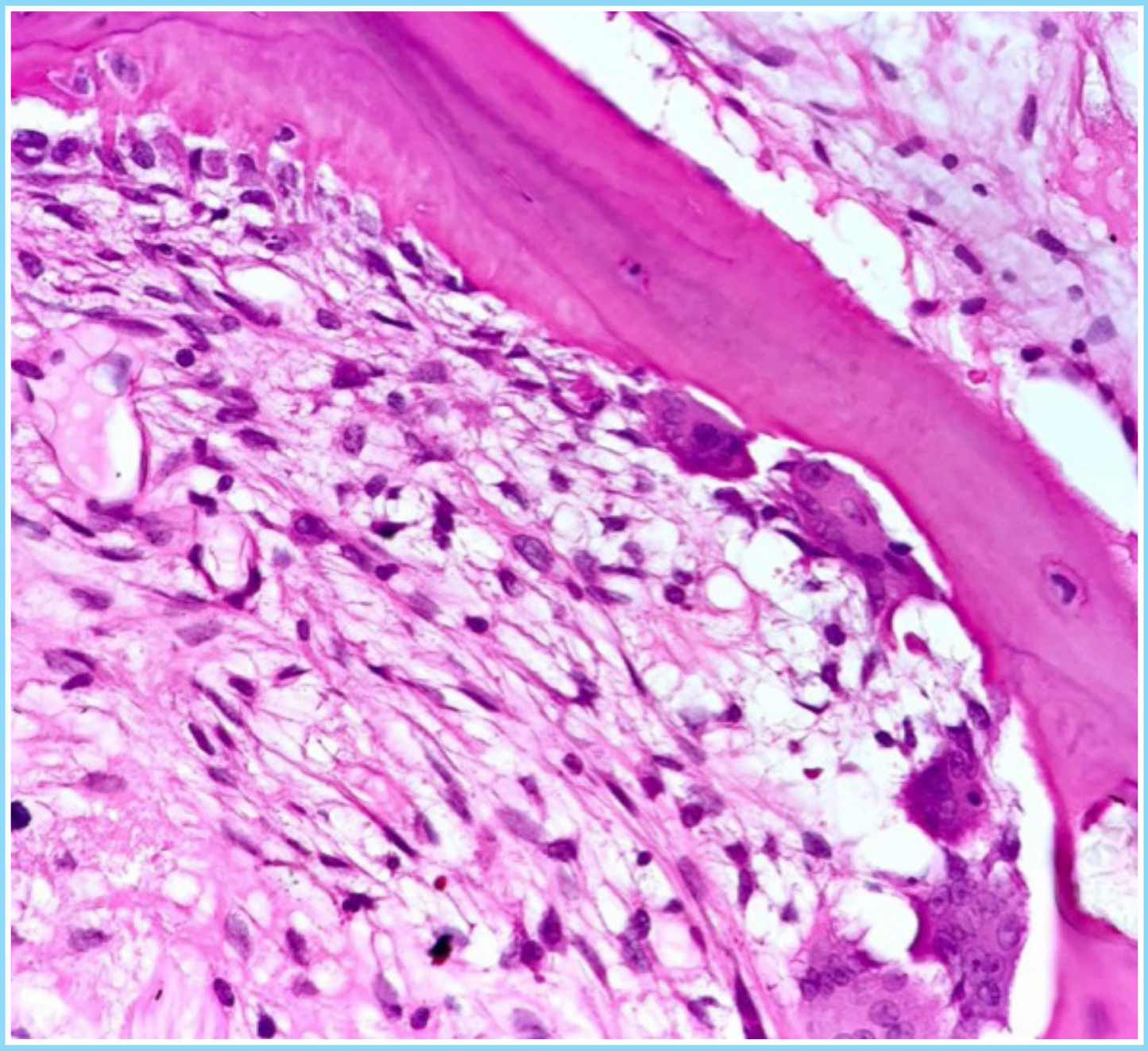

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Summary

Vol. **16** ■ April-June ■ **No.** 2

Originals

Special Article

Case Reports

Cover image:

Histological section of hip bone stained with hematoxylin and eosin, compatible with renal osteodystrophy.

Hernández Guevara J, Salcedo Rodríguez G, Felipe Varela A, Micolta Córdoba L, Marulanda Ibarra E, Felipe Kafury D. Challenges in the diagnosis and treatment of brown tumors - Clinical radiological features in a case series and review of the literature. Rev Osteoporos Metab Miner 2024;16(2):61-66

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Original

Management of vitamin D deficiency in clinical practice: results of a nationwide multidisciplinary study

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Abstract

Introduction: in recent years, there has been considerable interest in vitamin D, both regarding its physiological aspects and its deficiency, the need for supplementation, recommended doses, and even the type of metabolite that should be used.

Material and methods: given the lack of universally accepted criteria among all scientific societies and the significant heterogeneity observed in clinical practice regarding these issues, we conducted a survey of a sample of 698 doctors in Spain from the specialties of Primary Care, Internal Medicine, Rheumatology, Traumatology, Endocrinology, Gynecology, and Geriatrics to understand their opinions on various aspects of vitamin D management.

Results: there is a notable disparity in the responses to the 8 questions related to their usual clinical practice, both in the likelihood of requesting a vitamin D determination and in how it is prescribed.

Conclusion: finally, the recommendations of the expert panel that developed the survey and analyzed its results are presented.

Keywords:
Vitamin D. Survey. Spanish doctors.

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Gómez de Tejada Romero MJ, Torregrosa Suau Ó, Cancelo Hidalgo MJ, Martínez Díaz-Guerra G, Valdés y Llorca C, Tarazona Santabalbina FJ, Etxebarría Foronda Í, Sosa Henríquez M. Management of vitamin D deficiency in clinical practice: results of a nationwide multidisciplinary study. Rev Osteoporos Metab Miner 2024;16(2):33-47

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INTRODUCTION

The significant role of vitamin D in the prevention and treatment of clinical conditions, both skeletal and extraskeletal, as well as chronic diseases, along with the high prevalence of its deficiency worldwide, including developed countries with high solar exposure like Spain (1), has led to an increase in the demand for its analysis in recent years, both nationally and internationally (2-6). Additionally, there has been an increase in the prescription of vitamin D treatments (4-8). However, there is no unanimous consensus among medical societies, which provide different guidelines and recommendations depending on the degree of deficiency and the patient's profile (9-14), nor is there consensus on the optimal level of vitamin D, evaluated by the serum level of 25-hydroxyvitamin D (25[OH]D) (2,15,16), with ongoing debate about the cutoff value for defining deficiency, insufficiency, or overdose (17,18). Ultimately, although the decision on how to manage vitamin D deficiency is left to the health care professional's discretion, the determinants and characteristics of vitamin D prescription in routine clinical practice have been poorly investigated.

With this study, we aimed to evaluate the knowledge and prescription characteristics of vitamin D in the routine clinical practice of healthcare professionals in Spain and to assess whether there are differences in management among the various related specialties: Primary Care, Internal Medicine, Endocrinology, Traumatology, Gynecology, Rheumatology, and Geriatrics. To achieve this, we conducted a national survey with specific questions on the diagnosis, treatment, and monitoring of vitamin D deficiency.

MATERIALS AND METHODS

We conducted a non-interventional study based on an online quantitative survey from September through November 2022.

PARTICIPANTS

Medical specialists in Primary Care, Internal Medicine, Rheumatology, Traumatology, Endocrinology, Gynecology, or Geriatrics who practiced in the public or private national health care system and had, at least, 1 year of experience in managing patients with vitamin D deficiency. To participate, they were required to sign a consent form for the study.

QUESTIONNAIRE AND DATA MINING

The questionnaire included 8 closed-ended questions (some with multiple-choice options) on the diagnosis, treatment, and monitoring of vitamin D deficiency (Table I). This questionnaire was designed and agreed upon by a group of expert physicians in bone mineral metabolism and the specialties included in this study. Sociodemographic characteristics of the participants (specialty, age, gender, practice setting, and location) were also collected.

Health care professionals who met the inclusion criteria were contacted through a database of healthcare professionals (OneKey, IQVIA). Those who agreed to participate in the study accessed the questionnaire through the CAWI-NET platform.

The study was conducted in full compliance with the protocol, the principles established in the Declaration of Helsinki (19), the clinical practice guidelines on good pharmacoepidemiological practice, and quality procedures, and in compliance with relevant clinical practice guidelines on the treatment and protection of personal data. The study protocol was approved by Hospital Universitario Puerta de Hierro de Majadahonda Research Ethics Committee in Madrid, Spain (47/770284.9/22).

SAMPLE SIZE

Considering the universe of specialists, with a 95 % confidence level (p = q = 50 %), and the goal of not exceeding a 10 % sampling error in any of the consulted specialties, a total of 698 surveys were required: 110 in Primary Care, 100 in Internal Medicine, 98 in Endocrinology, 100 in Traumatology, 100 in Gynecology, 95 in Rheumatology, and 95 in Geriatrics. The representativeness of all geographical regions of the country was ensured. The national distribution by autonomous communities (ACs) was made proportionally to the universe under study. Subsequently, a geographical division into 5 zones (north, northeast, center, east, and south) was made for the corresponding subgroup analysis.

STATISTICAL ANALYSIS

All participants were identified with an anonymized code. Incomplete questionnaires were invalidated and replaced until the total sample of 698 was reached. No imputation of missing values was performed for any variable.

Both the number of cases and the percentage were used to describe categorical variables. The mean, standard deviation, median, quartiles (Q1 and Q3),

Table I. Questionnaire on the diagnosis, treatment, and monitoring of vitamin D deficiency

Questions	Answers
Q1. In your routine clinical practice, how relevant do you consider the identification of vitamin D deficiency states to be?	A. Very relevant B. Slightly relevant C. Not relevant at all D. DK/DA
Q2. If you decided to request a lab test for vitamin D levels…:	A. I could do it without any problem B. I could do it with difficulty, requiring justification and filling out forms C. I could not do it even if I wanted to D. DK/DA
Q3. When dealing with a patient who presents risk factors for vitamin D deficiency, when do you measure 25(OH) vitamin D levels to initiate treatment?	A. Always, to verify vitamin D deficiency before starting treatment B. Never. I treat suspected vitamin D deficiency without measuring 25(OH) blood levels C. Occasionally, depending on clinical circumstances or the metabolite being used D. DK/DA
Q4. At what levels of 25(OH)D do you consider vitamin D deficiency to be treated?	A. < 30 ng/mL B. < 20 ng/mL C. < 10 ng/mL D. DK/DA
Q5. What levels of 25(OH)D would you consider risky for adverse effects due to excess vitamin D activity (e.g., hypercalcemia, hypercalciuria, etc.)?	A. > 50 ng/mL B. > 60 ng/mL C. > 90 ng/mL D. DK/DA
Q6. Which of the following doses do you usually use? You may select multiple options:	A. Calcifediol 0.266 mg/month B. Calcifediol 0.266 mg/biweekly C. Calcifediol 0.266 mg/weekly D. Cholecalciferol 25,000 IU/month E. Cholecalciferol 25,000 IU/biweekly F. Cholecalciferol 25,000 IU/weekly G. Cholecalciferol 50,000 IU/weekly H. DK/DA
Q7. Do you think it is necessary to monitor vitamin D levels after starting treatment?	A. Only with calcifediol B. Only with cholecalciferol C. With either of the two D. With neither of the two E. DK/DA
Q8. If monitoring 25(OH)D levels, how often do you request a follow-up after the initial measurement?	A. Around 4 months B. Around 6 months C. Between 6 and 12 months D. I do not request follow-up tests E. DK/DA

DK/DA: does not know/does not answer.

minimum, and maximum were used to express continuous variables (age).

We conducted a descriptive analysis for the overall sample, as well as for each specialty. A comparative analysis was conducted between specialties, as well as between all specialties and Primary Care using the chi-square test. Within each specialty, sub-analyses were performed using the same methodology based on demographic characteristics: age (< 40 years / ≥ 40 years), gender, practice setting, and geographic location. Statistical analysis was performed using the Gandía BarbWin program. A *p*-value < 0.05 was considered statistically significant.

RESULTS

A total of 698 health care professionals successfully completed the survey and were included in the analysis. Table II shows the participants' sociodemographic characteristics. The participants' mean (standard deviation) age was 42 years (10.4), 56 % of whom were women, with some variations depending on the specialty. A total of 66.9 % practiced exclusively in the public sector, 7.4 % in the private sector, and 25.7 % in both sectors.

The answers to each question asked to respondents are shown in figure 1 and table III for the overall sample and broken down by specialties, respectively.

Most specialists surveyed stated that identifying states of vitamin D hypovitaminosis was very relevant (overall, 81 %). This consideration was significantly lower in Primary Care (72 %), Traumatology (69 %), and Gynecology (69 %) vs the other specialties (86 % up to 92 %) ($p < 0.05$).

Almost all professionals can request an analysis to determine 25(OH)D levels without restriction (overall, 95 %). Primary Care stands out as the specialty with the most difficulty in performing this determination: 12 % could do so with difficulty, while 1 % indicated they could not ($p < 0.05$ compared to other specialties).

Most specialties typically measure vitamin D levels before initiating treatment (always, 74 %; occasionally, 23 %; and never, 3 %).

Table II. Sociodemographic characteristics

	Primary Care (n = 110)	Internal Medicine (n = 100)	Endocrinology (n = 98)	Traumatology (n = 100)	Gynecology (n = 100)	Rheumatology (n = 95)	Geriatrics (n = 95)
Age	47.0 [10.3]	39.3 [8.4]	40.8 [9.7]	40.0 [9.0]	37.8 [9.3]	42.1 [10.7]	47.0 [11.0]
< 40 years	30 %	*67 %*	52 %	54 %	*71 %*	50 %	28 %
≥ 40 years	*70 %*	33 %	48 %	46 %	29 %	51 %	*72 %*
Gender							
Female	59 %	58 %	60 %	25 %	*78 %*	60 %	52 %
Male	41 %	42 %	40 %	*75 %*	22 %	40 %	48 %
Sector							
Public	*87 %*	72 %	66 %	48 %	55 %	73 %	65 %
Private	6 %	6 %	11 %	4 %	14 %	4 %	7 %
Mixed	7 %	22 %	22 %	*48 %*	31 %	23 %	27 %

Data are express as n *(%) or mean [standard deviation].*

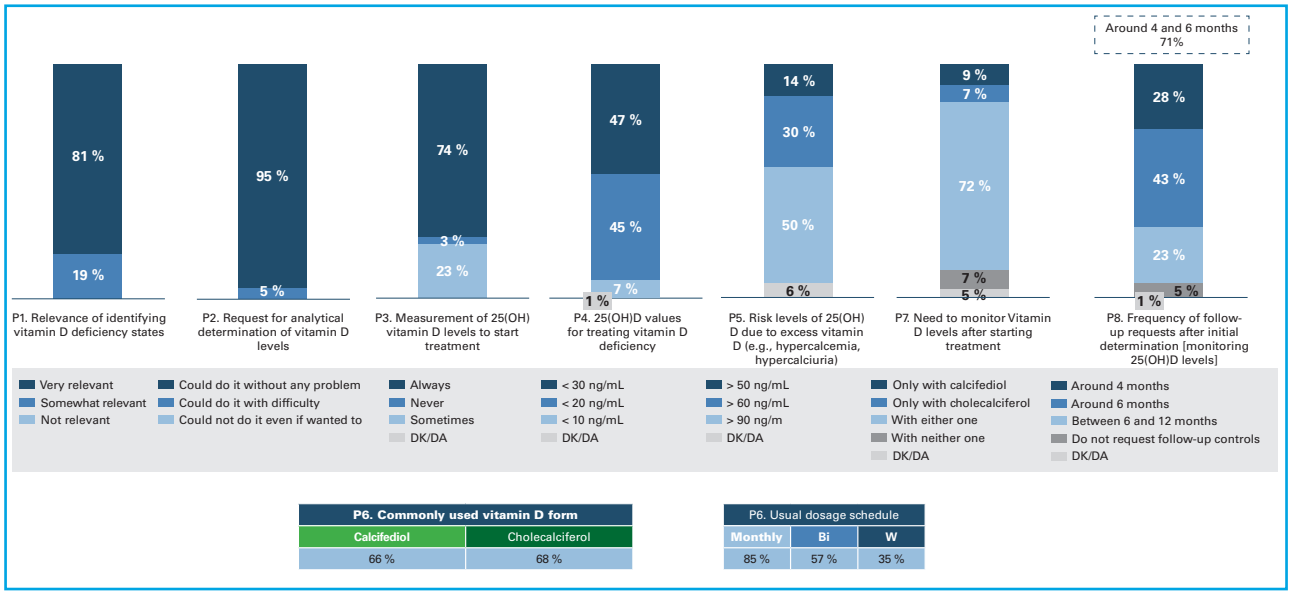

Figure 1. Issues related to the diagnosis, treatment, and monitoring of vitamin D deficiency. The results are presented for the total sample. Data are shown as a percentage. #Significant differences between periods ($p < 0.05$): W = weekly; Qi = biweekly; NS/NC: does not know/does not answer.

Table III. Issues related to the diagnosis, treatment, and monitoring of vitamin D deficiency

Survery	Primary Care (*n* = 110) A	Internal Medicine (*n* = 100) B	Endocrinology (*n* = 98) C	Traumatology (*n* = 100) D	Ginecology (*n* = 100) E	Rheumatology (*n* = 95) F	Geriatrics (*n* = 95) G
P1. Relevance of identifying vitamin D deficiency states							
- Very relevant	79 (72 %)	86 (86 %)*A,D,E	90 (92 %)*A,D,E	69 (69 %)	69 (69 %)	86 (91 %)*A,D,E	86 (91 %)*A,D,E
- Somewhat relevant	31 (28 %)*B,C,F,G	13 (13 %)	8 (8 %)	31 (31 %)	31 (31 %)	9 (9 %)	9 (9 %)
- Not relevant	0 (0 %)	1 (1 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 %	0 %
- DK/DA	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 %	0 %
P2. Request for analytical determination of vitamin D levels							
- Could do it without any problem	96 (87 %)	99 (99 %)*A	94 (96 %)*A	95 (95 %)	95 (95 %)	91 (96 %)*A	94 (99 %)*A
- Could do it with difficulty	13 (12 %)*B,C,F,G	1 (1 %)	4 (4 %)	5 (5 %)	5 (5 %)	4 (4 %)	1 (1 %)
- Could not do it even if wanted to	1 (1 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
- DK/DA	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
P3. Measurement of 25(OH) vitamin D levels to start treatment							
- Always	91 (83 %)*D,E	87 (87 %)*D,E,G	85 (87 %) *D,E,G	43 (43 %)	64 (64 %)*D	80 (84 %)*D,E,G	68 (72 %)*D
- Never	19 (17 %)	12 (12 %)	1 (1 %)	14 (14 %)*A,B,C,E,F,G	4 (4 %)*A,B,F	15 (16 %)	1 (1 %)
- Sometimes	0 (0 %)	1 (1 %)	12 (12 %)	43 (43 %)* A,B,C,F,G	32 (32 %)*A,B,C,F	0 (0 %)	26 (27 %)*B,C
- DK/DA	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
P4. 25(OH)D values for treating vitamin D deficiency							
- < 30 ng/mL	51 (46 %)*D	35 (35 %)	54 (55 %)*B,D	30 (30 %)	57 (57 %)*B,D	53 (56 %)*B,D	51 (54 %)*B,D
- < 20 ng/mL	52 (47 %)*G	56 (56 %)*E,F,G	43 (44 %)	54 (54 %)*E,G	36 (36 %)	39 (41 %)	31 (33 %)
- < 10 ng/mL	7 (7 %) *C	7 (7 %)	1 (1 %)	9 (9 %)*C	6 (6 %)	3 (3 %)	12 (13 %)*C,F
- DK/DA	0 (0 %)	2 (2 %)	0 (0 %)	7 (7 %)*A,C,E,F,G	1 (1 %)	0 (0 %)	0 (0 %)
P5. Risk levels of 25(OH)D due to excess vitamin D							
- > 50 ng/mL	20 (18 %)*D,F	19 (19 %)*D,F	12 (12 %)	6 (6 %)	12 (12 %)	8 (8 %)	22 (23 %)*C,D,E,F
- > 60 ng/mL	33 (30 %)*F	29 (29 %)	21 (21 %)	45 (45 %)*A,B,C,F,G	35 (35 %)*C,F	17 (18 %)	27 (28 %)
- > 90 ng/mL	48 (44 %)	46 (46 %)	64 (65 %)*A,B,D,E,G	35 (35 %)	41 (41 %)	68 (72 %)* A,B,D,E,G	44 (46 %)
- DK/DA	9 (8 %)*C	6 (6 %)	1 (2 %)	14 (14 %)*C,F,G	12 (12 %)* C,F,G	2 (2 %)	2 (2 %)

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Table III. Issues related to the diagnosis, treatment, and monitoring of vitamin D deficiency

Survery	Primary Care (*n* = 110) A	Internal Medicine (*n* = 100) B	Endocrinology (*n* = 98) C	Traumatology (*n* = 100) D	Ginecology (*n* = 100) E	Rheumatology (*n* = 95) F	Geriatrics (*n* = 95) G
P6A. Commonly used vitamin D form							
- Calcifediol 0.266 mg/month	62 (56 %)*,D,E	48 (48 %)*,D,E	63 (64 %)*,B,D,E	23 (23 %)	13 (13 %)	63 (66 %)*,B,D,E	60 (63 %)*,B,D,E
- Calcifediol 0.266 mg/Bi	38 (35 %)*,D,E	50 (50 %)*,A,D,E	64 (65 %)*,A,B,D,E	13 (13 %)	8 (8 %)	56 (59 %)*,A,D,E	58 (61 %)*,A,D,E
- Calcifediol 0.266 mg/W	14 (13 %)	20 (20 %)*,D,E	23 (24 %)*,A,D,E,F	8 (8 %)	6 (6 %)	12 (13 %)	14 (15 %)*,E
- Cholecalciferol 25,000 IU/month	46 (42 %)*,B,G	29 (29 %)	41 (42 %)*,G	35 (35 %)*,G	43 (43 %)*,B,G	51 (54 %)*,B,D,G	21 (22 %)
- Cholecalciferol 25,000 IU/Bi	38 (35 %)*,D	26 (26 %)	49 (50 %)*,A,B,D,E,G	18 (18 %)	30 (30 %)*,D	60 (63 %)*,A,B,D,E,G	24 (25 %)
- Cholecalciferol 25,000 IU/month	30 (27 %)*,B,G	12 (12 %)	24 (25 %)*,B	34 (34 %)*,B,F,G	44 (44 %)*,A,B,C,F,G	18 (19 %)	14 (15 %)
- Cholecalciferol 50,000 IU/month	10 (9 %)	8 (8 %)	9 (9 %)	6 (6 %)	3 (3 %)	6 (6 %)	4 (4 %)
- DK/DA	1 (1 %)	2 (2 %)	0 (0 %)	4 (4 %)*,C,F,G	2 (2 %)	0 (0 %)	0 (0 %)
P6B. Usual dosage schedule							
- Monthly	81 (74 %)*D,E,#,Q,S	64 (64 %)*,D,E,#,S	71 (72 %)*D,E,#,S	49 (49 %)#,Q	50 (50 %)#,Q	76 (80 %)*,B,D,E,G,#,S	64 (67 %)*,D,E,#,S
- Bi	59 (54 %)*D,E,#S	64 (64 %)*,D,E,#,S	78 (80 %)*,A,B,D,E,#,S	26 (26 %)	35 (35 %)	74 (78 %)*A,B,D,E,#,S	65 (68 %)*,A,D,E,#,S
- W	40 (36 %)	28 (28 %)	37 (38 %)	43 (43 %)*,B,F,G,#,Q	47 (47 %)*,B,F,G,#,Q	25 (26 %)	25 (26 %)
P7. Need to monitor Vitamin D levels after starting treatment							
- Only with calcifediol	7 (6 %)	9 (9 %)	9 (9 %)	9 (9 %)	6 (6 %)	9 (10 %)	15 % *E
- Only with cholecalciferol	8 (7 %)	9 (9 %)*C	22 (%)	15 (15 %)*C,G	9 (9 %)*C	6 (6 %)	3 %
- With either one	84 (76 %)*D,E	77 (77 %)*D,E	84 (86 %)*D,E	54 (54 %)	55 (55 %)	74 (78 %)*D,E	77 %*D,E
- With neither one	7 (6 %)*B	1 (1 %)	3 (3 %)	12 (12 %)*B,C	18 (18 %)*A,B,C,F,G	5 (5 %)	5 %
- DK/DA	5 (5 %)	4 (4 %)*C,G	0 (0 %)	10 (10 %)*C,F,G	12 (12 %)*A,B,C,F,G	1 (1 %)	0 %
P8. Frequency of follow- up requests after initial determination							
- Around 4 months	21 (19 %)	36 (36 %)*A	33 (34 %)*A	25 (25 %)	30 (30 %)	23 (24 %)	27 (28 %)
- Around 6 months	51 (46 %)*E	48 (48 %)*E	52 (53 %)*D	36 (36 %)	29 (29 %)	44 (47 %)*E	38 (40 %)
- Between 6 and 12 months	36 (33 %)*B,C,D	15 (15 %)	52 (13 %)	19 (19 %)	25 (25 %)*C	26 (27 %)*B,C	27 (28 %)*B,C
- > 12 months	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
- Do not request follow- up controls	1 (1 %)	0 (0 %)	0 (0 %)	16 (16 %)*A,B,C,F,G	15 (15 %)*A,B,C,F,G	0 (0 %)	3 (3 %)
- DK/DA	1 (1 %)	1 (1 %)	0 (0 %)	4 (4 %)*C	1 (1 %)	2 (2 %)	1 (1 %)
P1. Relevance of identifying excessive states of vitamin D							
- It is very important	79 (72 %)	*86 (86 %)*A,D,E*	*90 (92 %)*A,D,E*	69 (69 %)	69 (69 %)	*86 (91 %)*A,D,E*	*86 (91 %)*A,D,E*
- It is not that important	*31 (28 %)*B,C,F,G*	13 (13 %)	8 (8 %)	31 (31 %)	31 (31 %)	9 (9 %)	9 (9 %)
- It is not importat at all	0 (0 %)	1 (1 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 %	0 %
- DK/DA	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 %	0 %

(Continues on next page)

Table III. Issues related to the diagnosis, treatment, and monitoring of vitamin D deficiency

Survery	Primary Care (*n* = 110) A	Internal Medicine (*n* = 100) B	Endocrinology (*n* = 98) C	Traumatology (*n* = 100) D	Ginecology (*n* = 100) E	Rheumatology (*n* = 95) F	Geriatrics (*n* = 95) G
P2. Request for analytical determination of vitamin D levels							
- Could do it without any problem	96 (87 %)	*99 (99 %)*A*	*94 (96 %)*A*	95 (95 %)	95 (95 %)	*91 (96 %)*A*	*94 (99 %)*A*
- Could do it with difficulty, justifying it and filling out forms	*13 (12 %)*B,C,F,G*	1 (1 %)	4 (4 %)	5 (5 %)	5 (5 %)	4 (4 %)	1 (1 %)
- Could not do it even if wanted to	1 (1 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
- DK/DA	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
P3. Measurement of 25(OH) vitamin D levels to start treatment							
- Always, to verify that there is vitamin D deficiency before starting treatment	*91 (83 %)*D,E*	*87 (87 %)*D,E,G*	*85 (87 %)*D,E,G*	43 (43 %)	*64 (64 %)*D*	*80 (84 %)*D,E,G*	*68 (72 %)*D*
- Never. I treat the suspicion of vitamin D deficiency without measuring 25(OH) levels in blood	19 (17 %)	12 (12 %)	1 (1 %)	*14 (14 %)*A-G*	*4 (4 %)*A,B,F*	15 (16 %)	1 (1 %)
- In certain occasions, depending on clinical circumstances or the metabolite to be used	0 (0 %)	1 (1 %)	12 (12 %)	*43 (43 %)*A-G*	*32 (32 %)*A,B,C,F*	0 (0 %)	*26 (27 %)*B,C*
- DK/DA	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
P4. 25(OH)D values for treating vitamin D deficiency							
- < 30 ng/mL	*51 (46 %)*D*	35 (35 %)	*54 (55 %)*B,D*	30 (30 %)	*57 (57 %)*B,D*	*53 (56 %)*B,D*	*51 (54 %)*B,D*
- < 20 ng/mL	*52 (47 %)*G*	*56 (56 %)*E,F,G*	43 (44 %)	*54 (54 %)*E,G*	36 (36 %)	39 (41 %)	31 (33 %)
- < 10 ng/mL	*7 (7 %)*C*	7 (7 %)	1 (1 %)	9 (9 %)*C	6 (6 %)	3 (3 %)	*12 (13 %)*C,F*
- DK/DA	0 (0 %)	2 (2 %)	0 (0 %)	7 (7 %)*,A,C,E,F,G	1 (1 %)	0 (0 %)	0 (0 %)
P5. Risk levels of 25(OH)D due to excess vitamin D							
- > 50 ng/mL	*20 (18 %)*D,F*	*19 (19 %)*D,F*	12 (12 %)	6 (6 %)	12 (12 %)	8 (8 %)	*22 (23 %)*C,D,E,F*
- > 60 ng/mL	*33 (30 %)*F*	29 (29 %)	21 (21 %)	*45 (45 %)*A,B,C,F,G*	*35 (35 %)*C,F*	17 (18 %)	27 (28 %)
- > 90 ng/mL	48 (44 %)	46 (46 %)	*64 (65 %)*A,B,D,E,G*	35 (35 %)	41 (41 %)	*68 (72 %)*A,B,D,E,G*	44 (46 %)
- DK/DA	*9 (8 %)*C*	6 (6 %)	1 (2 %)	*14 (14 %)*C,F,G*	*12 (12 %)*C,F,G*	2 (2 %)	2 (2 %)

(Continues on next page)

Table III. Issues related to the diagnosis, treatment, and monitoring of vitamin D deficiency

Survery	Primary Care (*n* = 110) A	Internal Medicine (*n* = 100) B	Endocrinology (*n* = 98) C	Traumatology (*n* = 100) D	Ginecology (*n* = 100) E	Rheumatology (*n* = 95) F	Geriatrics (*n* = 95) G
P6A. Commonly used vitamin D form							
- Calcifediol 0.266 mg/month	*62 (56 %)*D,E*	*48 (48 %)*D,E*	*63 (64 %)*B,D,E*	23 (23 %)	13 (13 %)	*63 (66 %)*B,D,E*	*60 (63 %)*B,D,E*
- Calcifediol 0.266 mg/Bi	*38 (35 %)*D,E*	*50 (50 %)*A,D,E*	*64 (65 %)*A,B,D,E*	13 (13 %)	8 (8 %)	*56 (59 %)*A,D,E*	*58 (61 %)*A,D,E*
- Calcifediol 0.266 mg/W	14 (13 %)	*20 (20 %)*D,E*	*23 (24 %)*A,D,E,F*	8 (8 %)	6 (6 %)	12 (13 %)	*14 (15 %)*E*
- Cholecalciferol 25,000 IU/month	*46 (42 %)*B,G*	29 (29 %)	*41 (42 %)*G*	*35 (35 %)*G*	*43 (43 %)*B,G*	*51 (54 %)*B,D,G*	21 (22 %)
- Cholecalciferol 25,000 IU/Bi	*38 (35 %)*D*	26 (26 %)	*49 (50 %)*A,B,D,E,G*	18 (18 %)	*30 (30 %)*D*	*60 (63 %)*A,B,D,E,G*	24 (25 %)
- Cholecalciferol 25,000 IU/month	*30 (27 %)*B,G*	12 (12 %)	*24 (25 %)*B*	*34 (34 %)*B,F,G*	*44 (44 %)*A,B,C,F,G*	18 (19 %)	14 (15 %)
- Cholecalciferol 50,000 IU/month	10 (9 %)	8 (8 %)	9 (9 %)	6 (6 %)	3 (3 %)	6 (6 %)	4 (4 %)
- DK/DA	1 (1 %)	2 (2 %)	0 (0 %)	*4 (4 %)*C,F,G*	2 (2 %)	0 (0 %)	0 (0 %)
P6B. Usual dosage schedule							
- W	*81 (74 %)*D,E,#,Q,S*	*64 (64 %)*D,E,#,S*	*71 (72 %)*D,E,#,S*	*49 (49 %)#,Q*	50 (50 %)#,Q	*76 (80 %)*B,D,E,G,#,S*	*64 (67 %)*D,E,#,S*
- Bi	*59 (54 %)*D,E,#,S*	*64 (64 %)*D,E,#,S*	*78 (80 %)*A,B,D,E,#,S*	26 (26 %)	35 (35 %)	*74 (78 %)*A,B,D,E,#,S*	*65 (68 %)*A,D,E,#,S*
- W	40 (36 %)	28 (28 %)	37 (38 %)	*43 (43 %)*B,F,G,#,Q*	*47 (47 %)*B,F,G,#,Q*	25 (26 %)	25 (26 %)
P7. Need to monitor Vitamin D levels after starting treatment							
- Only with calcifediol	7 (6 %)	9 (9 %)	9 (9 %)	9 (9 %)	6 (6 %)	9 (10 %)	*15 %*E*
- Only with cholecalciferol	8 (7 %)	*9 (9 %)*C*	22 (%)	**15 (15 %)*C,G**	*9 (9 %)*C*	6 (6 %)	3 %
- With either one	*84 (76 %)*D,E*	*77 (77 %)*D,E*	*84 (86 %)*D,E*	54 (54 %)	55 (55 %)	*74 (78 %)*D,E*	*77 %*D,E*
- With neither one	*7 (6 %)*B*	1 (1 %)	3 (3 %)	*12 (12 %)*B,C*	*18 (18 %)*A,B,C,F,G*	5 (5 %)	5 %
- DK/DA	5 (5 %)	*4 (4 %)*C,G*	0 (0 %)	*10 (10 %)*C,F,G*	*12 (12 %)*A,B,C,F,G*	1 (1 %)	0 %
P8. Frequency of follow- up requests after initial determination							
- Around 4 months	21 (19 %)	*36 (36 %)*A*	*33 (34 %)*A*	25 (25 %)	30 (30 %)	23 (24 %)	27 (28 %)
- Around 6 months	*51 (46 %)*E*	*48 (48 %)*E*	*52 (53 %)*D*	36 (36 %)	29 (29 %)	*44 (47 %)*E*	38 (40 %)
- Between 6 and 12 months	*36 (33 %)*B,C,D*	15 (15 %)	52 (13 %)	19 (19 %)	25 (25 %)*C	*26 (27 %)*B,C*	*27 (28 %)*B,C*
- Do not request follow- up controls	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)
- DK/DA	1 (1 %)	0 (0 %)	0 (0 %)	*16 (16 %)*A,B,C,F,G*	*15 (15 %)*A,B,C,F,G*	0 (0 %)	3 (3 %)
	1 (1 %)	1 (1 %)	0 (0 %)	*4 (4 %)*C*	1 (1 %)	2 (2 %)	1 (1 %)

*The results are presented by specialty. The data are shown as percentages of the total number of respondents in each specialty. *A-G: Statistically significant differences between specialties (p < 0.05); #Significant differences between periods (p < 0.05); W: weekly; Bi: biweekly; DK/DA: does not know/does not answer.*

Traumatology and Gynecology stand out as the specialties that less frequently determine 25(OH)D levels systematically before starting treatment (Traumatology: 43 % occasionally and 14 % never; Gynecology: 32 % occasionally and 4 % never; $p < 0.05$ compared to other specialties).

Overall, a lack of consensus is evident regarding the cutoff point for treating vitamin D deficiency. A total of 47 %, 45 %, and 7 % consider 25(OH)D values of 30 ng/mL, 20 ng/mL, and 10 ng/mL, respectively, as the cutoff points for initiating treatment. In other words, 99 % would treat at levels < 10 ng/mL, 92 % < 20 ng/mL, and 47 % < 30 ng/mL. These percentages vary depending on the specialty consulted. Endocrinology, Gynecology, Rheumatology, and Geriatrics predominantly consider the value of 30 ng/mL (> 50 %). In contrast, internists and traumatologists more frequently (> 50 %) establish the threshold value at 20 ng/mL. Of note that 7 % of traumatologists indicated they did not know how to answer this question.

There is also a lack of consensus on the consideration of the risk of adverse effects due to excess vitamin D activity (e.g., hypercalcemia or hypercalciuria). Overall, the maximum acceptable 25(OH)D level is established at 50, 60, or 90 ng/mL by 14 %, 30 %, and 50 % of prescribers, respectively, that is, 14 % would warn of the risk of adverse effects due to excess vitamin D activity with values > 50 ng/mL, 44 % > 60 ng/mL, and 94 % > 90 ng/mL. Again, of note that 6 % of specialists did not know the answer to this question. These values vary depending on the specialty consulted. Rheumatology and Endocrinology predominantly consider the value of 90 ng/mL (> 50 %).

Both cholecalciferol and calcifediol are widely used molecules for the treatment of vitamin D deficiency (66 % and 68 % of professionals use them, respectively); the monthly regimen (65 %) is the most widely used vs the biweekly (57 %) and weekly (35 %) regimens ($p < 0.05$). Traumatology and Gynecology preferentially use cholecalciferol as the active ingredient ($p < 0.05$ vs calcifediol). They also make greater use of the weekly regimen ($p < 0.05$ vs other specialties) vs specialties such as Internal Medicine, Endocrinology, or Geriatrics. It is observed that among specialists who treat suspected vitamin D hypovitaminosis without measuring 25(OH)D levels in the blood, the use of cholecalciferol is significantly higher than that of calcifediol ($p < 0.05$).

In all specialties, it is considered necessary to monitor vitamin D levels after starting treatment (88 %, regardless of the active ingredient), generally between 4 and 6 months (71 %). However, Gynecology and Traumatology are the specialties that show the most divergence (15 % and 16 %, respectively, do not request follow-up checks; $p < 0.05$ vs other specialties).

Subgroup analyses were conducted based on the demographic characteristics of the participants (Annex 1). Some specialists aged ≥ 40 years showed divergences in certain aspects of vitamin D management vs their younger colleagues. Certain groups reported greater difficulty in requesting 25(OH)D tests, which was correlated with a significantly higher rate of empirical treatment (in the absence of testing).

DISCUSSION

Vitamin D deficiency is recognized as a major public health issue and is highly prevalent worldwide (20,21), even in Mediterranean countries like Spain (1). This has led to the implementation of food fortification programs and recommendations for supplementation and treatment of deficiency. Food fortification with vitamin D offers an opportunity to improve vitamin D intake in the population. However, in many countries, including Spain, fortification is voluntary and not widely implemented (22). The dosing of vitamin D can be complex due to different indications, various threshold values for treatment, available active ingredients, galenic instructions, dosages, and diverse clinical settings. This study aimed to evaluate the prescription practices of various medical specialties throughout Spain. A total of 698 specialists from 7 medical specialties participated in the study.

First, the results of our study demonstrate that medical specialists in Spain are aware of the clinical relevance of vitamin D deficiency (81 % consider hypovitaminosis D to be very relevant). The development of guidelines and growing scientific evidence have increased medical awareness of vitamin D and its possible supplementation to support general health and improve certain clinical conditions and chronic diseases observed in multiple specialties (8).

Nearly all professionals can request a test to determine 25(OH)D levels without restriction (overall, 95 %). This finding is certainly surprising, considering the screening protocols and strategies to limit vitamin D determinations (23,24), which can vary depending on the health care area. Although some specialties experienced greater difficulty in conducting determinations based on geographic location, these results did not follow a conclusive pattern.

Most specialties usually measure vitamin D levels to start treatment (74 % always, 26 % in certain cases or never). This finding highlights that vitamin D deficiency treatment is generally associated with analytically confirmed hypovitaminosis. The rate obtained is lower than similar studies conducted with primary care physicians on the treatment of institutionalized elderly patients (94 % began treatment after confirm-

ing hypovitaminosis D vs 83 % in our study) (25) or for the management of COVID-19 (26), but higher than a previous study conducted in Spain (55 % of *n* = 50 primary care physicians) (27).

However, there is a certain percentage of health care professionals who administer treatment in the absence of testing (empirical treatment). This result is similar to the work of Machattou et al. (30 % empirical treatment) (27). In this regard, various medical societies and health organizations already recommend starting vitamin D supplementation without testing in different populations, including the recommendations of the working group of the European Society of Clinical and Economical Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) (28). The underlying reasons for these recommendations are that there is sufficient evidence of the benefits, and this strategy is generally simple, effective, and economical. Examples include supplementation in individuals with insufficient sun exposure, children and adolescents, pregnant and breastfeeding women to meet the recommended daily amounts (28-31). The American Geriatrics Society indicates that 25(OH)D testing before starting treatment is unnecessary in older adults (≥ 65 years), especially if sun exposure is insufficient, as is the case with institutionalized elderly individuals (28,30,32,33). Various national and international societies also state that routine vitamin D screening may be unnecessary in patients with osteoporosis or fragility fractures, who should be prescribed vitamin D (often with calcium) as an adjunct to antiresorptive therapy (28,34). Cholecalciferol is recommended as the molecule of choice in cases where treatment is initiated without 25(OH)D testing (35,36).

Overall, a lack of consensus is evident regarding the threshold value for treating vitamin D deficiency. 47 %, 45 %, and 7 % of specialists consider 25(OH)D levels of 30 ng/mL, 20 ng/mL, and 10 ng/mL, respectively, as the thresholds for initiating treatment.

Heterogeneity in the responses aligns well with the lack of consensus among various organizations and scientific societies, which establish different concentrations for defining deficiency, insufficiency, or optimal vitamin D levels, also depending on the patient's profile (2,18,28,37). Regarding the minimum recommended value, an association has been described between serum 25(OH)D levels, bone mineral density (BMD), and musculoskeletal parameters. Some studies suggest that with levels < 20 ng/mL, there is an increased risk of fractures (28,38,39). Other studies point to 25(OH)D levels > 24 ng/mL to reduce the risk (40,41). From 30 ng/mL, parathyroid hormone (PTH) levels stabilize (42), significantly reducing the risk of falls and fractures (43). Higher levels may be necessary to achieve benefits beyond musculoskeletal health.

The controversy surrounding the definition of vitamin D deficiency and the maximum levels of 25(OH)D is partly due to the reporting of non-standardized results (44). Although it is widely accepted that measuring circulating 25(OH)D is the best indicator of an individual's vitamin D status (45), it is recognized that the 25(OH)D value obtained from a single sample can vary substantially depending on the assay used. Historically, 25(OH)D measurements were performed in research centers using high-pressure liquid chromatography (HPLC) or competitive protein-binding methods. In the 1990s, validated radioimmunoassays and other methods, such as enzyme-linked immunosorbent assay (ELISA) or chemiluminescence, were developed. The recent clinical availability of liquid chromatography-tandem mass spectrometry (LC-MS/MS) and HPLC technologies has improved the performance of 25(OH)D assays (46,47). Various standardization programs have also been developed: vitamin D External Quality Assessment Scheme (DEQAS) (48) or the Vitamin D Standardization Program (VDSP) (44). Despite these efforts, significant variability between and within assays persists to this day.

Of note that a considerable percentage of specialists believe that vitamin D deficiency should only be treated when values fall < 10 ng/mL, a level widely recognized as severe vitamin D deficiency and a patient risk (9,13,49-51).

Similarly, the maximum acceptable 25(OH)D level for considering the risk of adverse effects (e.g., hypercalcemia or hypercalciuria) was established at 50, 60, or 90 ng/mL by 14 %, 30 %, and 50 % of prescribers, respectively. There is also divergence in clinical practice guidelines, going from 50 up to 100 ng/mL, depending on the reference consulted (9,13,36,37,42,49,51,52). Although vitamin D toxicity is rare, it can present with severe hypercalcemia, hypercalciuria, and potential clinical signs, such as confusion, apathy, recurrent vomiting, abdominal pain, polyuria, polydipsia, or dehydration. This is related to excessive long-term vitamin D intake, the use of certain metabolites (as will be discussed later), metabolic pathway dysfunctions of vitamin D, or the presence of a concomitant disease that locally produces $1,25(OH)_2D$ (47). In addition to the described vitamin D toxicity, various clinical trials have shown that the risk of falls or mortality starts to increase moderately when 25(OH)D levels rise > 40-60 ng/mL, similar to what happens in deficiency situations (42,53,54). These observations are commonly referred to as the J or U curve effect and are already noted as non-physiological or "possibly harmful" levels by various national and international societies (13,28).

Both cholecalciferol and calcifediol are commonly used molecules for treating vitamin D deficiency (66 % and 68 % of professionals use them, respectively), with varying doses and regimens; the monthly regimen is the most used (65 %). The preference for the monthly regimen may reflect the dosing indications of national clinical practice guidelines for the treatment of

non-severe vitamin D deficiency (13,51). International clinical practice guidelines tend to recommend weekly treatment more often (11,34,52). However, the variety of reported doses and regimens indicates that physicians may adjust their choice based on the degree of deficiency, following recommendations (12,13,49,51).

It is observed that among specialists who treat suspected vitamin D deficiency without measuring 25(OH)D levels, the use of cholecalciferol is significantly higher than calcifediol ($p < 0.05$), possibly justified by its pharmacokinetic and safety profile. Pharmacokinetic studies have determined that the half-life of cholecalciferol is 60 days, as its lipophilic and fat-soluble nature allows for tissue storage (55-57). This characteristic of cholecalciferol would favor 25(OH)D production from tissue cholecalciferol according to the body's requirements (55).

The conversion rate of cholecalciferol to 25(OH)D follows a non-linear increase, resulting in a plasma 25(OH)D curve that plateaus at levels of approximately 30 to 50 ng/mL (56,59-64). In other words, there is a more significant increase (steeper curve) in serum 25(OH)D in cases of more severe vitamin D deficiency, and a lower conversion rate is observed once 25(OH)D levels approach a certain threshold or in patients with sufficient levels (58,59,61-64). This pharmacokinetic profile also prevents fluctuations in serum 25(OH)D after individual administrations; instead, sustained 25(OH)D levels are achieved over time (60). Overall, the hepatic hydroxylation stage (63,65), along with the non-linear production of 25(OH)D, can prevent an indefinite increase in serum values once under treatment and result in more predictable and stable levels over time at a given target level. In other words, evidence suggests that the efficacy of cholecalciferol supplementation in sufficient patients is physiologically reduced by the body, possibly to prevent overdose and toxicity.

Finally, all specialties consider it necessary to monitor vitamin D levels after starting treatment, generally between 4 and 6 months (71 %). This result is consistent with clinical practice guideline recommendations, which suggest monitoring serum concentrations every 3-4 months (13,14,32). A significant percentage delays this monitoring (6-12 months or does not request follow-up checks: 28 %). According to some clinical practice guidelines, monitoring may be deemed unnecessary in certain populations, as long as treatment is administered within recommended limits (13,32,34,66,67). Cases in which monitoring cannot be performed, medical societies have recommended the use of cholecalciferol (13,32), justified by the metabolism described earlier.

As far as we know, this survey is the first of its size at the national level, and also the first of international scope: these are its main strengths. The study design and sample size have ensured the geographic representativeness of specialists nationwide, as well as of each of the specialties included. However, it also presents limitations, as it did not include other specialties such as pediatrics, nor did it evaluate co-prescription with other treatments.

RECOMMENDATIONS FROM A MULTIDISCIPLINARY PANEL OF EXPERTS

Vitamin D deficiency has been widely linked to bone diseases such as rickets, osteomalacia, osteopenia, or osteoporosis. Various clinical trials evaluating the extra-skeletal effects of vitamin D have shown variable results, which have been associated with the inclusion of patients with sufficient levels. In fact, analyses in deficient patients have shown favorable outcomes in extra-skeletal conditions, such as cardiovascular risk, autoimmune diseases, diabetes, etc. Therefore, it seems generally advisable to maintain adequate vitamin D levels in the population (47).

Based on the results obtained in the present study, as well as the available scientific evidence, the multidisciplinary panel of experts made the following recommendations:

- At a multidisciplinary level, there are high-risk populations for vitamin D deficiency (49), such as people with muscle weakness or at risk of fractures/falls, in whom it would be indicated to determine 25(OH)D levels.
- There are patients who, due to their characteristics and clinical condition, could receive vitamin D treatment without the need for prior determination: limited sun exposure, insufficient vitamin D intake, pigmented skin, children and adolescents, pregnant and lactating women, older adults (≥ 65 years), and the elderly (especially if they are at risk of fractures), institutionalized individuals, subjects at risk of or diagnosed with osteoporosis, especially those receiving anti-osteoporotic treatment and those with fragility fractures, obese patients and those before/after bariatric surgery, malabsorption, and documented hypovitaminosis D, among others.
- Overall, intervals of 25(OH)D can be established to indicate vitamin D deficiency at < 20 ng/mL (< 50 nmol/L), insufficiency at 20-30 ng/mL (50-75 nmol/L), and an optimal range at 30-50 ng/mL (75-125 nmol/L). In any case, the target level may vary depending on the population group and the underlying clinical condition being treated with vitamin D. In the overall population, but especially in high-risk patients such as older adults, postmenopausal women, or patients with bone pathologies such as osteoporosis, it is suggested to maintain 25(OH)D levels above 30 ng/mL to maximize bone health benefits.
- Since mortality risk tends to increase slightly, it does not seem advisable to raise levels > 60 ng/mL.

– In general, either cholecalciferol or calcifediol can be used to treat patients with 25(OH)D deficiency, as both molecules have distinct pharmacokinetic and pharmacodynamic properties.
  • Due to the fact that treatments with cholecalciferol administered daily, weekly, or monthly are equally effective in achieving target serum concentrations, physicians should discuss with their patients which dosage regimen will achieve the best adherence. This equivalence has not been demonstrated for treatments based on calcifediol.
  • Calcitriol and active analogs of vitamin D should be reserved for populations with special pathologies, such as advanced renal failure or secondary hyperparathyroidism.
– If the health care professional decides to monitor 25(OH)D levels, it is recommended to do so 3-4 months after starting treatment and then every 6-12 months. If 25(OH)D levels are not determined or monitored, or if monitoring occurs at intervals > 6 months, treatment with cholecalciferol may be preferable due to its metabolism and plasma profile.
– Monitoring the levels of patients under treatment is advisable in the following situations: symptomatic vitamin D deficiency, use of metabolites other than cholecalciferol (e.g., calcifediol or calcitriol), supplementation in high doses (> 2000 IU/day in patients taking drugs that interfere with the absorption or metabolism of vitamin D or cause side effects), patients with poor adherence to treatment, a history of hypervitaminosis D, hypo- or hypercalcemia or hypercalciuria and hyperphosphatemia, malabsorption syndromes and bariatric surgery, obesity (body mass index > 30 kg/m^2), chronic granulomatous, liver, and renal diseases, metabolic bone diseases, particularly patients on anti-osteoporotic treatments or with a history of falls and fractures, hyperparathyroidism and hyperthyroidism, and patients hypersensitive to vitamin D, among others.
  • To maximize bone health, along with vitamin D supplementation, it is necessary to ensure a daily calcium intake of 1000-1200 mg, especially in patients with osteoporosis or at risk of falls or fractures. We suggest the combined use of calcium and vitamin D as an adjunct therapy to osteoporosis treatments.

CONCLUSION

In conclusion, the number of requests and treatments for vitamin D has increased in recent years. This study highlights the awareness that healthcare professionals already have regarding vitamin D deficiency. In turn, the survey identified some knowledge gaps among physicians and heterogeneity in the management of the deficiency, especially regarding threshold values and treatment monitoring. The results of this study offer insights for the development of national clinical guidelines, with recommendations based on scientific evidence.

ANNEX 1.

SUB-ANALYSIS OF GROUPS BASED ON DEMOGRAPHIC CHARACTERISTICS: AGE, GENDER, CLINICAL PRACTICE SETTING, AND GEOGRAPHICAL LOCATION

Some specialists aged 40 years or older show differences in certain aspects of vitamin D management vs their younger colleagues. In Rheumatology, a significantly higher proportion always measures levels before initiating treatment (94 % ≥ 40 years vs 75 % < 40 years; $p < 0.05$). In Traumatology, establishing 10 ng/mL (17 % ≥ 40 years vs 2 % < 40 years, $p < 0.05$) and 90 ng/mL (48 % ≥ 40 years v. 24 % < 40 years, $p < 0.05$) as cut-off points for treating vitamin D deficiency and a possible occurrence of adverse effects, respectively, is significantly more common.

Regarding the geographical location of health care professionals, of note that certain groups report greater difficulty in requesting 25(OH)D determinations: primary care providers in the northern and southern regions (14 % and 21 %, respectively, have difficulty; $p < 0.05$ vs other regions), as well as trauma specialists in the southern region (15 % have difficulty; $p < 0.05$ vs other regions). Consequently, different specialists perform empirical treatment (in the absence of determination) significantly more frequently: primary care providers in the northern region of Spain (36 % only measure levels on certain occasions), trauma specialists (30 % never), and gynecologists (55 % on certain occasions/never) in the southern region.

There were no statistically or clinically significant differences in other comparisons or categories.

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Original

Alteration of bone quality and prevalence of fragility fractures in patients with breast cancer treated with aromatase inhibitors. A case-control study

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Abstract

Purpose: to study the possible association between long-term treatment with aromatase inhibitors and deteriorated bone quantity and quality in postmenopausal women with breast cancer, leading to a higher prevalence of osteoporosis and fragility fractures.

Methods: case and control study. One hundred and four women with breast cancer who had been taking AIs for a median of 3 years were the cases and 104 women of similar age, height and weight made up the control group. We measured biochemical parameters of bone remodeling, vitamin D (25HCC) and PTH. Bone mineral density was determined by bone densitometry in the lumbar spine and in the proximal femur, and TBS in the lumbar spine. Finally, QUS parameters of the dominant foot were estimated.

Results: 46.3 % of patients had osteoporosis compared to 16.1 % of controls 38.4 % of these women had suffered at least one fragility fracture, compared to 20.1 % of controls. Women with AI had lower values of bone mass as well as QUS and TBS. Only 9.6 % of women receiving AI had optimal 25HCC levels (greater than 30 ng/mL) compared to 20.2 % of controls. In the logistic regression analysis, the variables associated with the presence of fragility fractures were the time taking AI, vitamin D levels, TBS and beta-crosslaps (CTX). TBS correlated with QUI ($r = 0.754$. $p < 0.01$).

Conclusions: AIs cause a decrease of bone mass and an alteration in bone quality which increase the risk of fractures. After having had AI for at least 3 years, 46.3 % had densitometric osteoporosis and 38.4 % had suffered at least one fragility fracture. Less than half of the patients had prescribed calcium and vitamin D and less than 20 % some drug for osteoporosis.

Keywords:
Breast cancer.
Osteoporosis.
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Artificial intelligence: the authors declare not to have used artificial intelligence (AI) or any AI-assisted technologies in the elaboration of the article.

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INTRODUCTION

Breast cancer is the most common tumor in women in the world today, regardless of their age, with its peak incidence occurring between 50 and 69 years of age (1). Worldwide cancer incidence and mortality rates for 2020 were an estimated 19.3 million new cases of cancer and almost 10.0 million deaths. The most commonly diagnosed cancers were female breast cancer with 2.26 million cases (2). Moreover, its high incidence and prevalence of long-term survivors has highlighted the need to study the long-term effect that some treatments may have on the quality of life of these patients (3).

Osteoporosis is also a very prevalent disease, estimated to affect more than 200 million patients worldwide. About one in 3 women after menopause will suffer a fragility or osteoporotic fracture. The wrist, vertebra and hip are the most common fractures (4).

About 70-80 % of early breast cancer patients receive adjuvant endocrine therapy (ET) for at least 5 years and either at the beginning or at another time of treatment these treatments include including gonadotropin-releasing hormone (GnRH) agonists. chemotherapy-induced ovarian failure (CIOF) and aromatase inhibitors (AIs). All these drugs can cause bone loss and increase fracture risk (5).

Most of the published articles on women treated with aromatase inhibitors report loss of bone mass and increased risk of fragility fracture, but few have studied the alteration that these drugs can produce in bone quality. This fact led us to carry out this work.

METHODS

In this case-control study, patients with breast cancer who have received at least 3 years of treatment with aromatase inhibitors are considered cases. The control patients are women of a similar age who did not have breast cancer. We administered a questionnaire to all patients to collect clinical data designed for the purpose.

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. The blood was collected in the appropriate specific tubes for each determination with as little venous compression as possible and was centrifuged at 1,500 g for 10 minutes. Serum was separated into aliquots and stored within one hour of extraction at -20 °C until biochemical analyzes were performed. Glucose, urea, creatinine, calcium, inorganic phosphorus and total proteins were measured using standardized and automated colorimetric techniques in an autoanalyzer (Kodak Ektachem Clinical Chemistry Slides). Most measurements were carried out the same day of the extraction. Serum calcium was corrected according to total protein using the following formula: Corrected calcium = previous calcium (mg/dl)/[0.55 + total protein (g/l)/16]. Tartrate-resistant acid phosphatase (TRAP) was determined by spectrophotometry. Glomerular filtration rate (GFR) was calculated using the MDRD formula (Modification of Diet in Renal Disease) (6). Renal failure was considered with GFR values below 60 ml/m/m^2 (7). Serum levels of 25(OH) vitamin D (25HCC) were measured by immunochemiluminescence. according to the Nichols method (Nichols Institute Diagnostics. San Clemente, California, USA). This method has an intra-assay coefficient of variation of 3.0-4.5 % and inter-assay of 7.1-10.0 %. The values given by the laboratory as normal range between 10 and 68 ng/ml. Serum parathormone (PTH) concentrations for the intact molecule were determined by immunochemiluminescence, according to the Nichols Advantage assay. The normal range in adults is between 6 and 40 pg/ml. with an inter-assay coefficient of variation of 7.0-9.2 %. Type I collagen amino-terminal propeptides (P1NP) and beta-crosslaps in blood were measured by previously described techniques (8,9). The remaining biochemical parameters were determined by colorimetric techniques.

CALCANEUS ULTRASOUND DETERMINATION (QUS)

Ultrasonographic parameters were estimated in the calcaneus of the dominant foot using a Sahara Hologic® ultrasonography (Bedford, Massachusetts, USA). This device measures both Broadband Ultrasound Attenuation (BUA) and Speed of Sound (SOS) in the targeted calcaneal region. The BUA and SOS values are combined into a single parameter called the Quantitative Ultrasound Index (QUI), also known as stiffness, 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 (10).

BONE MINERAL DENSITY (BMD)

This was measured by dual X-ray absorptiometry (DXA). both in the lumbar spine (L2-L4) and in the proximal end of the femur with a Hologic Discovery® densitometer (Hologic Inc. Waltham, Massachusetts, USA). Its accuracy is 0.75-0.16 %. Measurements were

made by the same operator. Therefore, there was no inter-observer variation. The T-score values were calculated from the values published as normal for the Canary Island population (11).

TRABECULAR BONE SCORE (TBS)

All TBS measurements were performed using the TBS iNsight Software. version 2.0.0.1 (Med-Imaps, Pessac, France). The computer program uses the image previously obtained by DXA in the same region of interest of the L2-L4 lumbar spine. The T-score values were calculated from the reference values obtained for the Spanish population (12).

ETHICS

The study was conducted following the standards of the Declaration of Helsinki (13) and was approved by the Ethics Committee of the Hospital Insular de Gran Canaria (Spain). All patients were informed of the objectives of the study and their informed consent was requested.

STATISTICAL ANALYSIS

The categorical variables were summarized using percentages and the numerical variables using means and standard deviations. To study the possible associations between categorical variables, the chi-square test of independence was used and as a measure of association, the odds ratio (OR) with a 95 % confidence interval (95 % CI). In those cases in which there were cells with less than 5 cases, Fischer's exact test was used. To evaluate the association between a quantitative variable and a categorical variable. Student's t-test or ANOVA (if there were more than 2 categories) was used for normally distributed variables or the non-parametric Mann-Whitney U test for non-normal. The normal distribution of values was verified with the Kolmogorov-Smirnov test. Student's t test for paired and unpaired observations or Wilcoxon test and Mann-Whitney test were used as appropriate. The degree of association between two variables was verified by Spearman's coefficient. Logistic regression analysis using a retrospective method based on the Akaike's information criterion was performed to study the association between fractures and the study variables. The resulting model was summarized in *p*-values and adjusted odd ratios which were estimated by 95 % CIs. Statistics were performed with SPSS program (Statistic Package for the Social Sciences, v.25.0) and statistical significance was set at $p < 0.05$.

RESULTS

This is a case-control study where women who had suffered breast cancer and who had received at least 3 years of AI treatment were considered cases, and controls were women with the same age and similar height and weight without breast cancer. Table I shows the baseline characteristics of both groups. Current calcium intake and prevalence of rheumatoid arthritis were similar in both groups with no statistically significant differences. Conversely, the prevalence of fragility fractures was significantly higher in women with breast cancer and treated with AIs. both in total fractures (38.4 % vs 20.1 %) and in vertebral fractures (26.9 % vs 14.4 %) and non-vertebral fractures (15.3 vs 7.6 %). Some patients had both vertebral and non-vertebral fractures so the total sum exceeds that of fractures.

Table II shows the results obtained when analyzing BMD. Patients with breast cancer, treated with AI, were found to have less BMD in each and every one of the anatomical locations where DXA was carried out, the differences being statistically significant in all cases. We consider the existence of densitometric osteoporosis when the T-score < -2.5 in any of the 3 locations: lumbar spine, femoral neck or total hip. 46.3 % of patients with breast cancer and treated with AI had osteoporosis compared to 16.1 % of the control group ($p = 0.01$).

The quality of the vertebral trabecular connections was also estimated by calculating the TBS, which showed lower values in patients with breast cancer and treated with AI (1.313 g/cm^2 ± 0.112 vs 1.452 g/cm^2 ± 0.109. $p = 0.01$). The prevalence of patients with normal TBS, considering this as a value greater than 1,313 g/cm^2, was only 25.1 % compared to 65.4 % of the women in the control group ($p = 0.01$), predominating in patients with breast cancer and treated with AI a partially degraded TBS, between 1,200 -1,350 g/cm^2, in 44.2 % of the cases compared to 25.7 % in the women of the control group, $p = 0.01$.

QUS showed lower values in women treated with AI compared to controls (QUI: 71.3 ± 12.6 vs 77.2 ± 15.4, $p = 0.03$, BUA 53.9 ± 10.6 db/mgHz vs 57.8 ± 11.2 and SOS 1,501 ± 0.6 m/s vs 1,521 ± 24) $p = 0.04$. We obtained a statistically significant correlation between TBS values in the lumbar spine and QUI in the calcaneus ($r = 0.754$, $p < 0.001$) (Fig. 1).

Table III shows the biochemical values related to bone mineral metabolism. Renal function was similar in both groups, as well as calcium, phosphorus, and total serum protein, with no statistically significant differences between the two groups. Women receiving AI showed higher serum levels of some biochemical markers of remodeling, especially indicators of osteoclastic activity, such as CTX and TRAP with statistically significant differences, as well as osteocalcin ($p < 0.05$ in all cases).

Table I. Baseline characteristics of the study population

	Patients	Controls	*p* value
Number	104	104	
Age (years)	62.2 ± 9.3	62.1 ± 9.2	0.800
BMI (kg/m^2)	27.6 ± 5.2	28.7 ± 4.3	0.583
Current calcium intake (mg/day)	651.7 ± 295	569 ± 272	0.406
Rheumatoid arthritis *n* (%)	2 (3.8)	5 (4.8)	0.542
Fragility fractures *n* (%)*	40 (38.4%)	21 (20.1 %)	0.001
Vertebral fractures *n* (%)*	28 (26.9)	15 (14.4)	0.001
Non-vertebral fractures *n* (%)*	16 (15.3)	8 (7.6)	0.004
Years receiving AIs (median. IQ95)	3 (2-5)		
Indicated osteoporosis treatment (%)**	18 (17.3)	24 (23)	0.04
Indicated calcium and vitamin D (%)	45 (43.2)	57 (54.8)	0.03

**The sum does not match because some patients had vertebral and non-vertebral fractures. ** Any treatment: bisphosphonates, SERMs, denosumab...*

Table II. Densitometric parameters. Quantitative and qualitative ultrasounds

	Patients	Controls	*p* value
DXA			
L2-L4 g/cm^2	0.792 ± 0.128	0.864 ± 0.252	0.01
Tscore	-2.4 ± 1.2	-1.7 ± 1.5	0.01
Femoral neck g/cm^2	0.674 ± 0.131	0.712 ± 0.125	0.03
Tscore	-1.5 + 1.2	-1.1	0.03
Total hip g/cm^2	0.897 ± 0.201	1.000 ± 0.147	< 0.05
Tscore	-2.1 ± 1.3	0.5 ± 1.1	< 0.05
Trabecular bone score (TBS)	1.289 ± 0.114	1.359 ± 0.109	0.001
Tscore	-2.3 ± 1.2	-1.2 ± 0.8	0.01
TBS > 1.313 g/cm^2 *n* (%)	26 (25.1)	68 (65.4)	
TBS between 1.350-1.200 g/cm^2 *n* (%)	42 (44.2)	27 (25.7)	0.01
TBS < 1.200 g/cm^2 *n* (%)	32 (30.7)	9 (8.9)	
Osteoporosis* *n* (%)	46.3%	16.1%	0.01
QUS			
QUI	71.3 ± 12.6	77.2 ± 15.4	0.03
Tscore	-1.7 ± 0.8	-1.4 ± 0.9	0.03
BUA (db/mgHz)	53.9 ± 10.6	57.8 ± 11.2	0.04
Tscore	-1.5 ± 0.6	-1.2 ± 0.7	0.04
SOS (m/s)	1,501 ± 18	1,521 ± 24	0.04
Tscore	-1.6 ± 0.7	-1.3 ± 0.8	0.04

**The existence of osteoporosis was considered when the Tscore value was less than -2.5 in any of the 3 anatomical locations (lumbar spine L2L4, femoral neck or total hip).*

We did not obtain statistically significant differences in serum P1NP values, a parameter that indicates osteoblastic activity, nor in serum PTH levels. Vitamin D was determined by its metabolite 25HCC. Women with breast cancer receiving AI had lower vitamin D levels than controls (21.6 ± 9.7 ng/mL vs 25.6 ± 12.5 ng/mL, $p < 0.001$). Only 9.6 % of women receiving AI had optimal 25HCC levels (above 30 ng/mL) while almost half were below 20 ng/mL, the limit that indicates deficiency, compared to 20.2 % of the controls who had 25HCC values above 30 ng/mL.

When carrying out a multidimensional logistic regression study, we found the variables that were statistically significantly associated with the presence of fragility fractures in women receiving AI were, firstly, the time they had been receiving this drug, followed by the serum levels of beta-crosslaps while serum levels of vitamin D, measured as 25HCC, and TBS were negatively associated (lower levels of these variables increased the risk of fracture and vice versa, $p < 0.05$ in all cases).

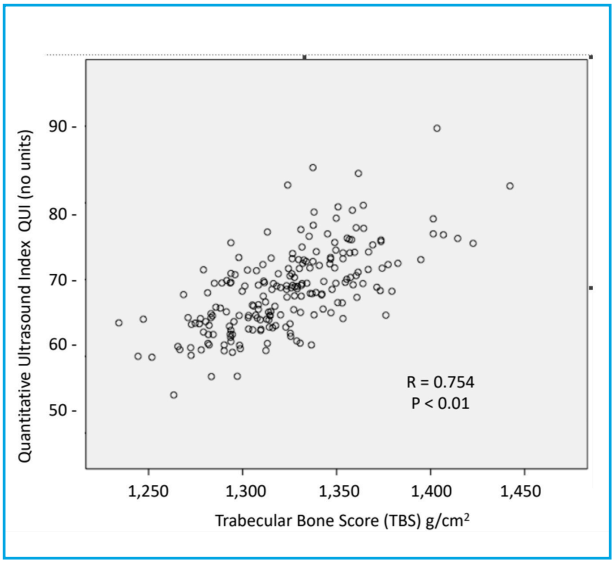

Figure 1. Correlation between QUI and TBS.

Table III. Biochemical and bone mineral metabolism parameters

	Patients	Controls	*p* value
Creatinin (mg/dL)	0.7 ± 0.4	0.9 ± 1.2	0.564
GFR (ml/m/m²)	81.5 ± 12.3	83.6 ± 11.5	0.441
Calcium (mg/dL)	9.4 ± 0.6	9.5 ± 0.7	0.871
Phosphorus (mg/dL)	4.2 ± 0.8	4.3 ± 0.7	0.856
Corrected calcium (mg/dL)	9.4 ± 0.6	9.4 ± 0.7	0.267
Total proteins (g/L)	7.2 ± 0.9	7.3 ± 0.7	0.824
Osteocalcin (ng/mL)	38.9 ± 10.5	17.2 ± 16.8	0.015
P1NP (mg/dL)	32.1 ± 12.7	26.4 ± 18.6	0.07
Beta-crosslaps (CTX) (ng/mL)	0.62 ± 0.34	0.21 ± 0.23	0.001
TRAP (IU/L)	3.7 ± 2.4	1.8 ± 2.1	0.021
PTH (pg/mL)	62.5 ± 12.6	55.1 +14.6	0.276
25HCC (ng/mL)	21.6 ± 9.7	25.6 ± 12.5	0.001
Normal > 30 ng/mL	10 (9.6 %)	21 (20.2 %)	0.001
Insuficiency 20-30 ng/mL	46 (44.3 %)	44 (42.3 %)	
Deficiency < 20 ng/mL	48 (46.1 %)	39 (37.5 %)	

P1NP: procollagen type I aminoterminal; TRAP: tartrate-resistant acid phosphatase; PTH: parathyroid hormone; 25HCC: 25-hidroxicholecalciferol.

DISCUSSION

Aromatase inhibitors are a group of drugs used in the first line of treatment for breast cancer, especially those with positive hormone receptors (14,15). Their use has made it possible to significantly increase the survival of these patients, but they also have notable secondary effects. These include loss of bone mass (16) and increased risk of fragility fractures (14,15,17-21). Thus, the literature shows that in postmenopausal women AIs increase bone turnover and induce bone loss at sites rich in trabecular bone at an average rate of 1-3 % per year which is at least 2-fold higher than bone loss seen in healthy, age-matched postmenopausal women (14,15,22). All of which results in a significantly higher fracture incidence regardless of the AI administered.

The time that the women have been taking AIs seems to be decisive both in the appearance of loss of bone mass and in the risk of suffering a fragility fracture (5,14,18,22,23). Our patients had been receiving an AIs

for a minimum of 3 years, as a criterion for inclusion in the study, and more than 25 % had been receiving the drug for 5 years. Almost 40 % of the patients in our study had suffered at least one fragility fracture at the time of evaluation and 46.3 % had osteoporosis densitometrically, with or without fragility fractures. Even so, less than half (43.2 %) had indicated a calcium and vitamin D supplement and less than 20 % of these same patients had prescribed a drug for the treatment of osteoporosis (17.3 %). We must highlight that of the 43.2 % who had indicated the calcium and vitamin D supplement, 30 % took it irregularly or did not take it at all. These data are unacceptable and force us to try to establish a work protocol in our environment so that all patients with breast cancer who receive treatment with AI are protocolized and undergo at least one bone densitometry at the start of treatment as has been reported (24,25) and indicating at least a calcium and vitamin D supplement. Moreover, the need to be monitored for bone mineral metabolism and receive follow-up as is done with other diseases, such as anticoagulation with dicoumarinics.

Bone densitometry is the current standard-of-care screening tool for fracture risk is bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) and the most widely used technique (26,27). A decreased bone mineral density (BMD) is a strong risk factor for fractures, and measuring BMD by dual-energy X-ray absorptiometry (DXA) is the gold standard tool for diagnosing osteoporosis. In patients receiving AI, the risk of suffering a fragility fracture has been associated with the loss of bone mineral density produced by this group of drugs (15,17).

Various studies have shown the loss of BMD associated with the use of AIs. In this sense, our patients have shown lower values of bone mineral density in all anatomical locations in which we have performed the determination of bone mass: lumbar spine, L2L4, femoral neck and total hip, compared to women in the control group.

Several studies using quantitative ultrasound (QUS) have generally found good correlation with DXA, prevalent vertebral fractures and risk of future fractures (28-31). QUS is able to predict incident fractures, independently from DXA, possibly by indicating more and different information on the physical properties of bone tissue (eg, structure and elasticity affect ultrasound transmission) that contribute to bone strength and are not recognized by DXA (29,32-35). We have found only two publications from the group of Catalano et al (36,37) relating the QUS to bone quality in patients receiving AI, measuring the QUS in the phalanges of the fingers and none in which the QUS in the calcaneus. Our results show that patients who have received AIs for a minimum of 3 years have an alteration in bone quality, determined by QUS in the calcaneus. The values of all the ultrasonographic parameters, SOS, BUA and QUI, are lower in the women of the group treated with AIs compared to those of the control group, $p < 0.05$ in all cases. To complete the assessment of bone quality, we have done TBS measurements on our patients in the lumbar spine. TBS is a novel gray-level texture measurement based on standard DXA images which correlates with three-dimensional parameters of bone texture and that provides further information on bone strength additional to the standard BMD (38,39). Differently from BMD it may be less affected by spinal degenerative changes (40) and has been shown to be an independent indicator of increased fracture risk and its application improves the 10-year fracture risk prediction attained by FRAX® when considering that patients receiving AIs have a secondary cause of osteoporosis, the risk of fracture increases markedly, which possibly constitutes a better approximation to reality (18,41). In a study similar to ours carried out by Catalano et al. (36,37), they obtained a prevalence of patients who had a TBS with grade 2, between 1,350 and 1,200 greater than 60 % and grade 3, with a TBS < 1,200 of 10 %, similar to our results.

On the other hand, we have obtained a statistically significant correlation between QUI and TBS ($r = 0.754$, $p < 0.01$) as shown in figure 1. Both parameters have been shown to be good indicators of bone quality.

AIs have a marked antiestrogenic action and this produces, at the level of bone metabolism, an increase in bone remodeling at the expense, above all, of an increase in the activity of osteoclasts (15,17,20). This has been shown in our patients, since the group that received AIs for at least 3 years presented an increase in biochemical markers of bone remodeling, CTX and TRAP, as well as osteocalcin. In all cases, these are statistically significant differences. This would indicate a greater bone resorption that would lead to loss of quantity and deterioration of bone quality, which was confirmed by DXA as well as by TBS and QUS.

We determined vitamin D levels by measuring its metabolite 25-hydroxycholecalciferol (25HCC) and found that women affected by breast cancer who received AI had lower 25HCC levels than controls (21.6 ± 9.7 vs 25.6 12.5 ng/mL, $p < 0.01$). Interestingly, less than 10 % of AI-treated women presented 25HCC levels considered optimal (> 30 ng/mL) (42), but this same fact was observed in 20.2 % of the women in the control group. This confirms that most of the women who were part of the study present vitamin D insufficiency as described in other patient groups or even in populations of healthy women (43,44). On the contrary, we did not obtain statistically significant differences in PTH values between both groups. Finally, we observe in table IV that when analyzing a multidimensional logistic regression model, the variables that had a statistically significant association with the presence of fragility fractures were the time they received AIs (each year of treatment doubled the risk of having a fracture) and in-

Table IV. Multidimensional logistic regression model of variables with independent association with the presence of fractures in women with breast cancer

Variable	*p* value	OR (95 % CI)
Time on treatment with AIs (per year)	0.001	2.021 (1.478; 2.794)
Beta-crosslaps (per ng/mL)	0.001	1.921 (1.470; 2.471)
25 (OHD) (per ng/mL)	0.01	0.347 (0.238; 0.507)
TBS (per g/cm^2)	0.04	0.619 (0.406; 0.941)

creased beta-crosslaps or CTX, a marker of bone destruction (8). A decrease in 25HCC levels and TBS values were also associated with the presence of fragility fractures. Our study has several limitations. First, its sample size is relatively small, with just over 100 cases in each group. This was due to the rigor with which we included the patients in each group: they had to have received AIs for at least 3 years without interruption, with the absence of other diseases that could affect the bone. Also, the control group had to be made up of women of similar age, height and weight without breast cancer, which limited the inclusion of controls. Another limitation is that we have collected all the aromatase inhibitors in a single group when differences in their effect on bone mineral metabolism have been described among them. Thus, Exemestane, having a certain androgenic effect, seems to induce a lower loss of bone mineral density (15). We have not been able to carry out an analysis of the different groups of drugs, because the number of patients included in each one would be very small, but it is a continuing line of research.

In conclusion, 38.4 % of women affected by breast cancer who received prolonged treatment with AIs had at least one fragility fracture, and 36.3 % had densitometric osteoporosis. Even so, less than half were prescribed calcium and vitamin D and less than 20 % received any medication for osteoporosis. In these patients, it is advisable to include in their study protocol the performance of a bone densitometry and indicate treatment from the moment they have had a fragility fracture or without them, when this risk is high.

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Special Article

Dialogues between basic and clinical researchers: hypophosphatasia

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Abstract

Most serum alkaline phosphatase (ALP) (> 90 %) originates from the liver and bone. Normally, the contribution from other tissues, such as the intestine or kidney, is much smaller, although the placenta is an important source during pregnancy. Elevated ALP levels are usually indicative of liver or bone disease.

The analysis of other liver enzymes, particularly GGT—which is elevated in liver damage and normal in bone diseases—usually clarifies the origin. When in doubt, the bone isoform can be measured, or a profile of all isoenzymes can be conducted.

Keywords:
Alkaline phosphatase. Biomarker. Hypophosphatasia. ALPL. Genetics.

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ALKALINE PHOSPHATASE: BIOMARKER OF HYPOPHOSPHATASIA AND OTHER DISORDERS

Most of the serum alkaline phosphatase (ALP) (over 90 %) comes from the liver and bones. Normally, the contribution from other tissues, such as the intestine or kidney, is much smaller, although the placenta is an important source during pregnancy. Therefore, elevated ALP levels are usually indicative of liver or bone disease. The analysis of other liver enzymes, particularly γ-glutamyltransferase (GGT)—elevated in liver injury and normal in bone diseases—usually clarifies the origin. When in doubt, the bone isoform can be measured, or a profile of all isoenzymes can be conducted.

A decrease in ALP is a frequent transient finding in various acute diseases. More sustained decreases can be seen in various systemic disorders, such as celiac disease, myeloma, severe anemia (especially due to vitamin B_{12} deficiency), or various conditions associated with a slowdown in osteoblastic activity, such as hypoparathyroidism, hypothyroidism, hypercortisolism, certain skeletal abnormalities associated with advanced kidney disease, or treatment with antiresorptive drugs (bisphosphonates or denosumab). For being active, the ALP molecule requires the binding of certain cofactors, so the deficiency of cations such as zinc, magnesium, or calcium can be associated with a decrease in its serum activity (1).

If these acquired causes are excluded, a genetic cause for the ALP decrease should be considered. Among the hereditary diseases associated with low ALP are cleidocranial dysplasia and Wilson's disease. The associated abnormalities of the clavicles and liver, respectively, usually help in correctly diagnosing these rare disorders (Table I). If clinical and lab test results do not support these diagnoses and no secondary acquired cause is identified, low serum ALP levels may be indicative of the patient exhibiting hypophosphatasia (HPP) related to a mutation in the *ALPL* gene, which encodes the tissue-nonspecific ALP (TNSALP), including the liver and bone isoforms. Although these isoforms—encoded by the same gene—share the amino acid sequence, they differ in some post-translational modifications, such as glycosylation patterns.

However, when the coding regions of the *ALPL* gene are sequenced, variants are observed in only about 60 % of patients with low ALP (2). In other cases, the cause of low ALP levels remains unclear. Perhaps this decrease is related to other genomic or epigenomic changes or to post-translational changes of the protein (3).

A useful parameter for confirming ALP deficiency is the determination of pyridoxal 5-phosphate (PLP) in plasma. This is the main circulating form of vitamin B_6 and is hydrolyzed by ALP, so when ALP activity is deficient, the levels of PLP go up. Of note that PLP levels depend on vitamin B_6 intake. Therefore, they may increase if the patient is on vitamin supplements. Conversely, levels may be normal or even low—despite the patient having an ALP deficiency—if there is an associated vitamin B_6 deficiency (4). Hence, PLP determination is not a perfect diagnostic test; nevertheless, it can be very helpful, especially if it is not possible to sequence the *ALPL* gene.

Pathogenic variants of the *ALPL* gene lead to HPP, a disorder with a varied clinical spectrum. Infantile forms are usually severe with a a pronounced rickets-like condition, as ALP is necessary for bone mineralization. In adults, signs are usually much milder. They often present as stress fractures, chondrocalcinosis, tendinopathies, or dental abnormalities (5,6). Some patients may be completely asymptomatic, making it difficult to distinguish cases with mild signs from those who are simply "asymptomatic carriers" of the genetic variant. Therefore, the diagnosis of HPP requires the integration of clinical, biochemical, and genetic data, as we have recently reviewed (3). In any case, caution should be exercised in the use of antiresorptive drugs—particularly bisphosphonates—in these patients, as it has been suggested—although not clearly demonstrated yet—that they may have a higher risk of atypical fractures (7).

Table I. Causes of persistent decrease in serum alkaline phosphatase

Acquired causes
Hormonal
Hypoparathyroidism
Hypothyroidism
Hypercortisolism
Drugs
Bisphosphonates
Denosumab
Corticosteroids
Clofibrate
Vitamin D (toxicity)
Nutritional
General malnutrition
Vitamin deficiencies (C and B_{12})
Mineral deficiencies (calcium, zinc, and magnesium)
Other diseases
Celiac disease
Multiple myeloma
Advanced kidney failure
Genetic
Hypophosphatasia
Cleidocranial dysplasia
Wilson's disease
Acrodermatitis enteropathica
Hemochromatosis

Treatment of patients with HPP with moderate clinical signs, as is generally the case in adult-onset cases, is generally symptomatic. However, in cases with severe signs, particularly in children and adolescents, enzyme replacement therapy with asfotase alfa may be indicated. This is a soluble glycoprotein of 726 amino acids obtained by cell engineering, combining the active part of TNSALP, the Fc domain of human IgG1, and a deca-aspartate peptide domain (8,9). Although some criteria for its use in adults have been suggested (10), and some studies with small groups of patients have provided promising results (11), its role after growth is completed is less established.

ALKALINE PHOSPHATASE AND HYPOPHOSPHATASIA: MOLECULAR MECHANISMS

The *ALPL* gene encoding TNSALP is located on chromosome 1p34-36 (12) and is expressed in various tissues, including bones, liver, and kidney (13). TNSALP is an ectoenzyme that binds to the plasma membrane through a glycosylphosphatidylinositol (GPI) anchor molecule (12). Its main function is to catalyze the hydrolysis of phosphomonoesters (14), such as PLP, inorganic pyrophosphate (PPi), adenosine triphosphate (ATP), diphosphorylated lipopolysaccharide (LPS), and phosphorylated osteopontin (p-OPN), releasing inorganic phosphate (12,15-17). TNSALP requires 2 Zn^{2+} ions and 1 Mg^{2+} ion to form as a homodimer (18) and work properly (19).

Regarding the genetics of HPP, it has been demonstrated that the *ALPL* gene has great allelic heterogeneity (12). According to ALPL (https://alplmutationdatabase.jku.at) and LOVD variant databases (https://databases.lovd), about 500 loss-of-function variants of the *ALPL* gene have been reported (20). This great allelic heterogeneity is related to a very variable clinical expression of HPP (20,21), leading to the categorization of HPP into different clinical forms, from the most severe to the mildest: lethal perinatal HPP, infantile HPP, childhood-onset HPP, adult HPP, odontohypophosphatasia, and benign perinatal HPP (22,23).

HPP can be inherited in an autosomal dominant or recessive manner. The more severe clinical phenotypes are transmitted as a recessive autosomal trait, while milder forms may result from recessive or dominant transmission. However, cases of adult HPP with a mutation in only one allele and a more severe phenotype may be found. These cases could be explained by the presence of other intronic mutations or mutations in the regulatory sequence or by the existence of a heterozygous mutation with a dominant negative effect (24,25). This can lead to a decrease in the activity of the wild-type monomer in the heterodimeric enzyme complex, altering the structural and functional properties of TNSALP. Approximately 13.4 % of the alleles identified in HPP patients have a dominant negative effect in the European population (26). Examination of the TNSALP 3D model reveals that the protein consists of 3 distinct areas: the active site (including the 3 metal binding points), the homodimer binding zone, the crown domain (involved in functions such as non-competitive inhibition, thermal stability, allosteric behavior, dimer stability, and collagen binding), the calcium binding domain (whose function is not yet fully understood), and the N-terminal alpha-helix (which contributes to the stability of the dimeric structure). Most mutations that have been experimentally shown to have a measurable dominant negative effect are found in the homodimer binding region, the active site, and the crown domain (20).

As mentioned earlier, it can be difficult to interpret cases with persistently low ALP levels without identifying pathogenic variants in the *ALPL* gene. Of note that, in addition to those already mentioned, there are other less common situations that can also decrease bone formation and, therefore, be associated with low ALP levels. For example, iron and ferritin have been shown to be potent inhibitors of osteogenesis, significantly inhibiting ALP activity. The ferroxidase activity of ferritin is thought to be central to this inhibition (27). Furthermore, other factors are involved in the regulation of ALP, such as the transcription factor RUNX2 (28), as well as other regulators of Pi levels, such as PHOSPHO1 or ENPP1, which acts as a phosphatase in the absence of TNSALP (1). In this context, the existence of other modifier genes related to the development of heterogeneous clinical signs in patients with decreased ALP levels cannot be ruled out. Additionally, epigenetic changes could contribute to the severity of clinical signs in patients with HPP. In this regard, DNA methylation has been shown to play an important role in regulating ALPL expression (29). Similarly, different lifestyles or behaviors appear to have a direct effect on ALP levels. Thus, physical activity has been directly related to increased ALP levels (30,31). Therefore, for studying the phenotype associated with HPP, it would seem reasonable to explore the role of these regulatory factors as well as the contribution of external factors, such as lifestyle. In any case, in patients with clinical and biochemical findings consistent with HPP, it would be interesting to perform whole-genome sequencing to identify possible mutations in the regulatory or non-coding regions of the *ALPL* gene, as well as possible mutations in other genes regulating the ALP activity. Additionally, functional studies should be conducted to characterize each genetic variant to explore the relationship with specific phenotypes to better understand the possible effects of these variants in the carrier patient. Although it is difficult to establish a genotype-phenotype correlation in HPP patients, the correct identification of new variants and the study of their phenotype would improve our understanding of this metabolic disorder, making it accessible to the scientific community, which would allow for better management of the disease.

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Case Report

Challenges in the diagnosis and treatment of brown tumors – Clinical radiological features in a case series and review of the literature

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Abstract

Introduction: brown tumors result from changes in bone metabolism due to primary, secondary, or tertiary hyperparathyroidism. Their significance lies in the increased risk of pathological fractures, pain, disability, and functional limitation they can cause.

Case reports and discussion: this case series report presents 3 patients with secondary hyperparathyroidism due to chronic kidney disease (CKD) who had not been diagnosed or treated and had sustained pathological fractures. These cases were presented at a referral hospital in southwestern Colombia. The clinical, radiological, and surgical characteristics are described. Additionally, a critical literature review is conducted on secondary CKD-related hyperparathyroidism to emphasize the importance of diagnostic suspicion, as nearly 1 in 3 patients with advanced-stage CKD will develop secondary hyperparathyroidism, leading to a high risk of pathological fractures associated with significant morbidity.

Keywords:
Brown tumors. Osteitis fibrosa cystica. Secondary hyperparathyroidism. Pathological fractures.

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INTRODUCTION

Brown tumors are the result of excessive osteoclastic activity and consist of accumulations of osteoclasts and giant cells within fibrous tissue. This phenomenon is the outcome of a metabolic bone disease triggered by primary, secondary, or tertiary hyperparathyroidism (HPT) (1).

They may be considered an enigmatic and infrequent clinical entity due to advances in the diagnosis of CKD and hyperparathyroidism since the beginning of the 21st century. Similarly, their early diagnosis is rare since there are no protocols for their detection in patients with CKD (2). The direct association between hyperparathyroidism and bone metabolism disease dates back to 1925 when Mandl performed the first parathyroidectomy described in the literature, demonstrating improvement of bone lesions in patients with osteitis fibrosa cystica, a disease of which brown tumors are a severe and localized sign (1,3).

Incidence rates are reported to be higher in men, with a ratio of 3:1 vs women, and are more common in patients older than 50 years (4). They can occur anywhere but are more common in the facial bones, ribs, clavicles, pelvis, and femur (5).

Clinically, most are asymptomatic but can cause swelling, a sensation of a mass, and even pain, especially when associated with pathological fractures. Depending on their location, they can cause radicular pain or, in some cases, have been reported to cause cauda equina syndrome and paraparesis (6,7).

The main focus of treatment revolves around identifying and addressing the underlying cause of hyperparathyroidism through surgical resection or pharmacological management aimed at restoring the function of the parathyroid glands responsible for the excessive production of parathyroid hormone (PTH) (8). In cases in which brown tumors cause pathological fractures, a surgical procedure is usually required to stabilize the affected bone.

Given the uniqueness of brown tumors, their clinical significance is notable. This case series presents 3 cases of brown tumors associated with secondary hyperparathyroidism due to chronic kidney disease, 2 of which cases showed that the initial clinical sign of hyperparathyroidism was the presence of a pathological fracture. The third case involves a patient who presented without fractures but with pain in the lower extremity, followed by a CT scan that revealed the presence of an osteolytic lesion, and later sustained an associated pathological fracture. These cases were managed at a referral hospital in southwestern Colombia in 2023.

CASE REPORTS

The patients included in this series met the following criteria:

1. Clinical documentation of hyperparathyroidism.
2. Documentation of the presence of brown tumors, excluding the possibility that these lesions were due to bone metastases.
3. Presence of an associated pathological fracture.

CASE REPORT #1

A 39-year-old man with a 10-year history of chronic kidney disease due to polycystic kidney disease, on renal replacement therapy for the past 9 years on a 3 times per week regimen, with nephrology follow-up every 4 months. However, he reports difficulty accessing health care due to remote residence and socioeconomic conditions. Additionally, he has a 15-year history of hypertension and left hip fracture due to high-impact trauma from a traffic accident, which was surgically treated with a short cephalomedullary nail.

He fell from his own height, sustaining a direct trauma to his left hemipelvis and leg, resulting in an inability to stand, left thigh pain, and deformity. Upon admission to the center, a biochemical profile was obtained, revealing significant hypercalcemia and markedly elevated PTH (2306 pg/mL).

An anteroposterior X-ray of the left femur showed the previously described hip osteosynthesis material, a large osteolytic lesion involving the middle and distal thirds of the femur with a displaced diaphyseal fracture of the distal third of the left femur (Fig. 1). These findings confirmed the presence of hypercaptation in the skull, mandible, axial, and appendicular skeleton, with absence of renal silhouettes, and lytic lesions in the left femur and right tibia with an associated pathological fracture in the left femur.

The patient underwent open reduction, biopsy, and internal fixation of the fracture (Fig. 1). Immunohistochemical staining confirmed the suspected diagnosis. Subsequently, a parathyroidectomy was performed. However, the patient developed hungry bone syndrome with a fatal outcome.

CASE REPORT #2

A 66-year-old woman with a 15-year history of chronic kidney disease due to diabetic nephropathy, on a 10-year regimen of renal replacement therapy. Additionally, she had a history of hypertension, dyslipidemia, osteopenia, and moderate dependency

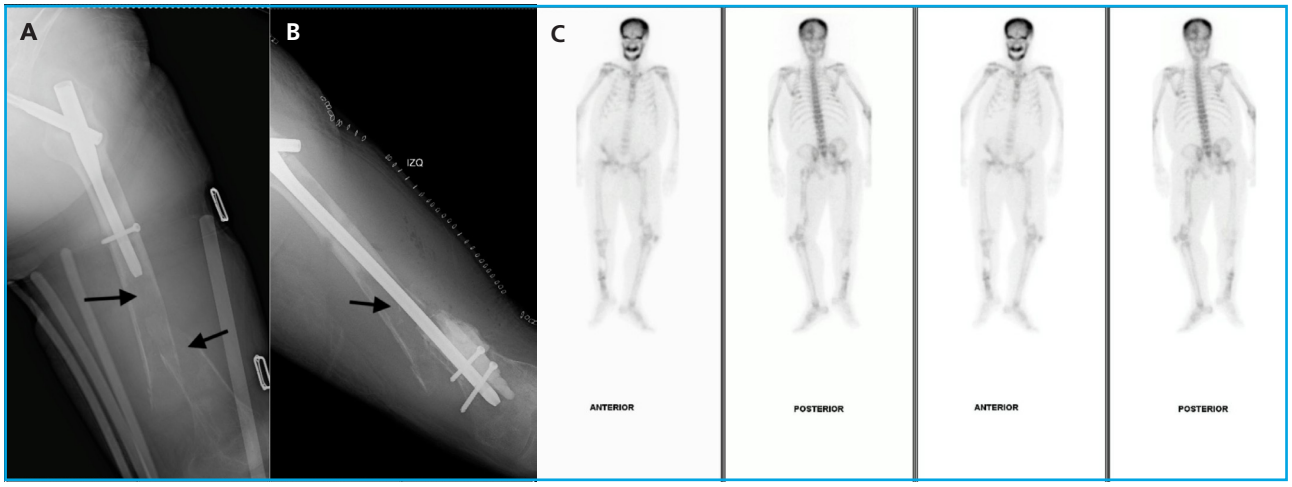

Figure 1. A. Plain X-ray of the left femur in an anteroposterior projection showing a diaphyseal fracture and osteolytic lesions at the fracture site. B. Plain X-ray of the postoperative femur. C. Bone scan performed with technetium showing hypercaptation in the skull, jaw, axial, and appendicular skeleton.

for activities of daily living (Barthel index, 65 points; Lawton and Brody scale, 6 points) due to sequelae from a fall 5 years prior with trauma to the left hemibody. However, she reports not seeking hospital care due to socioeconomic difficulties. Her family notes that after 1 year of being bedridden, she was gradually able to walk with a walker.

She fell from her own height, sustaining trauma to the right hemibody, resulting in right groin pain, inability to stand, and inability to mobilize the right lower limb.

She was admitted to the ER with a 2 cm shortening of the right lower limb vs the contralateral limb, and the affected limb was externally rotated. An anteroposterior X-ray of the pelvis revealed an old untreated fracture in the left femur with signs of callus formation and varus deformity, and a Garden III intracapsular transcervical fracture of the right hip with an osteolytic lesion in the greater trochanter of the left femur (Fig. 2A). Afterwards, due to the osteolytic lesion, the contrast-enhanced CT scan of the hip revealed the above-mentioned fracture with callus formation in the left hip and the transcervical fracture of the right hip (Fig. 2A). Given the patient's past medical history, further tests were performed, revealing PTH levels of 1560 pg/mg.

An orthopedic oncology consultation was requested due to the presence of osteolytic lesions that posed a risk of pathological fractures, and given the patient's age, bilateral total hip arthroplasty was recommended. However, due to surgical risk and multiple comorbidities, a decision was made to perform right hip arthroplasty in the first surgical act. Postoperatively, with contralateral hip pain, an X-ray was revealed the presence of a well-positioned right hip prosthesis and a transcervical refracture of the left hip associated with an osteolytic lesion in the ipsilateral proximal metaphysis that had gone unnoticed (Fig. 2B). Left hip arthroplasty was performed uneventfully, and the postoperative X-ray revealed well-positioned bilateral hip prostheses (Fig. 2B).

The femoral heads were sent for histopathological examination, which reported renal osteodystrophy, confirming the suspected diagnosis of a brown tumor. Four days after surgery, the patient began experiencing intense pain in her left knee without associated trauma, which prompted a femur X-ray that revealed the presence of a fracture in the distal metaphysis of the ipsilateral femur (Fig. 2B). A left knee X-ray revealed the presence of an osteolytic lesion in the left femur distal metaphysis with an associated pathological fracture (Fig. 2B). The CT scan of the left knee revealed multiple lytic lesions in the distal femoral metaphysis and diaphysis (Fig. 2B).

The primary pathology was prioritized, and the patient was evaluated by endocrinology and head and neck surgery, who considered her eligible for parathyroidectomy. However, the patient refused surgical treatment and signed a voluntary hospital discharge form.

CASE REPORT #3

A 33-year-old woman with an 8-year diagnosis of chronic kidney disease due to lupus nephropathy, on a 4-year regimen of renal replacement therapy, with

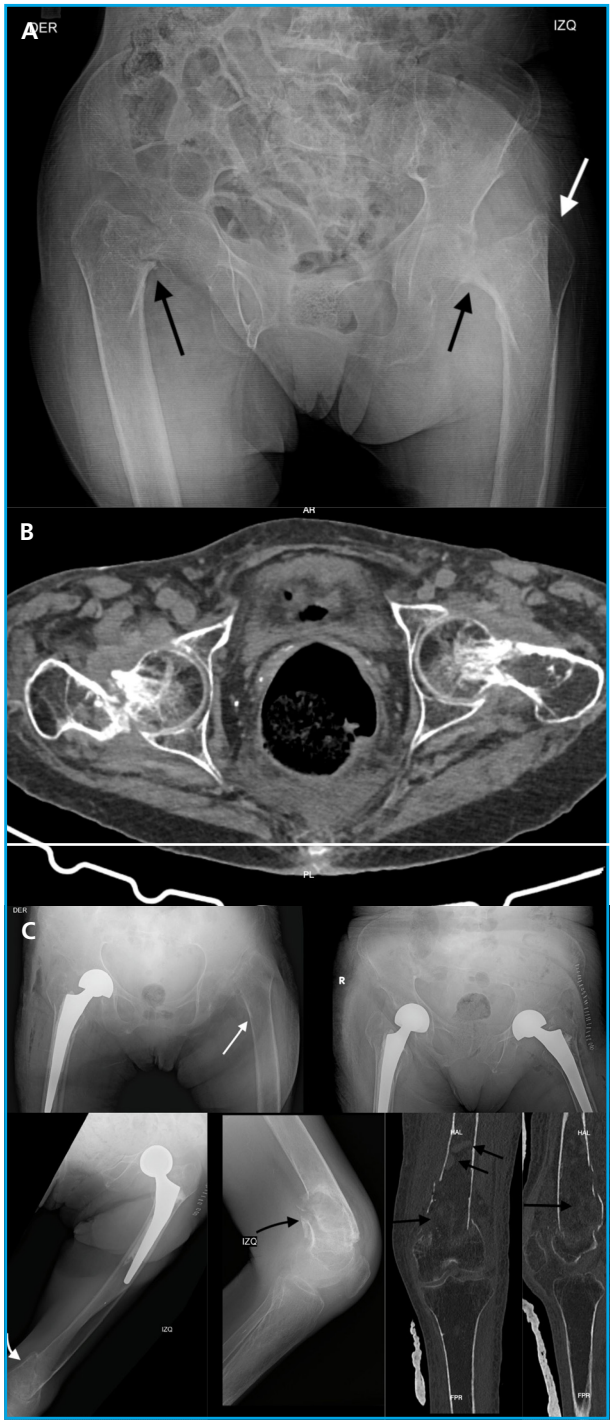

Figure 2. Panel A (upper): anteroposterior plain X-ray of the pelvis. Old fracture in the left femur and signs of callus formation with varus deformity. Transcervical intracapsular fracture of the right hip (Garden III) with an osteolytic lesion in the greater trochanter of the left femur. Panel A (lower): axial CT scan of the hip. Transverse section. Panel B (upper left): plain X-ray of the pelvis with a total right hip replacement. Transcervical refracture of the left hip. Panel B (upper right): bilateral hip replacement. Panel B (lower left): lateral plain X-ray of the knee showing lytic lesions. Panel B (lower right): transverse section of an axial CT scan of the knee.

the last lupus flare 5 months prior to the clinical presentation.

She presented to the orthopedic outpatient clinic with a 4-month history of persistent pain in the proximal region of her right thigh, with increased volume vs the contralateral side, but without limitation in passive or active range of motion. The comparative hip CT scan revealed the presence of an osteolytic lesion in the proximal right femur (Fig. 3), with high suspicion of secondary hyperparathyroidism due to chronic kidney disease given her history. However, due to the patient's age and low risk of pathological fractures

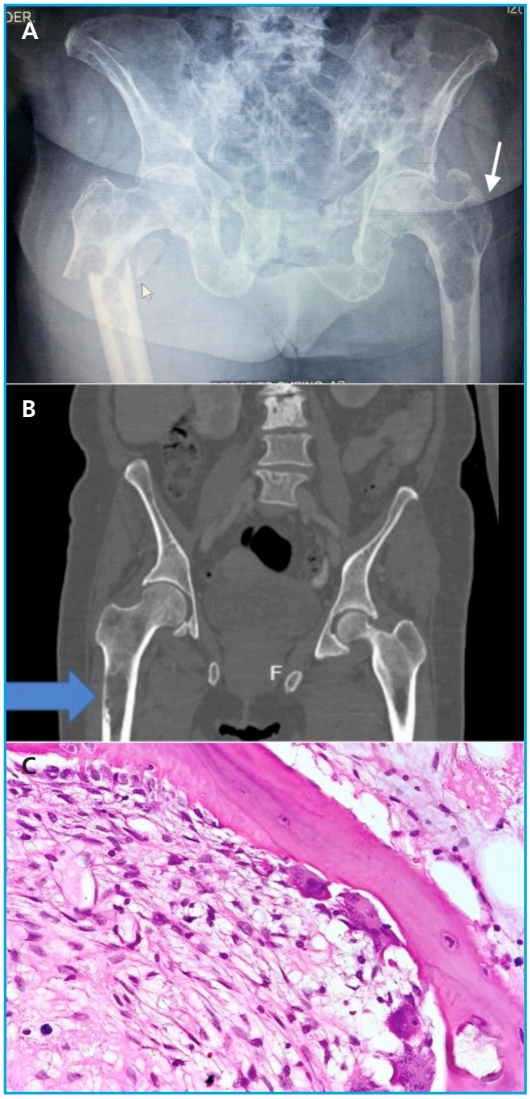

Figure 3. A. Anteroposterior plain X-ray of the pelvis showing a subtrochanteric fracture of the right femur and an osteolytic lesion in the greater trochanter of the contralateral femur. B. Comparative hip CT scan showing an osteolytic lesion in the right proximal femur. C. Histological section of hip bone stained with hematoxylin and eosin, compatible with renal osteodystrophy.

calculated by extrapolation of the Mirels scale—originally used for bone metastases—surgery was initially deemed unnecessary.

However, given the patient's socioeconomic condition, which hindered periodic follow-up, she was admitted through the ER, evaluated by Nephrology and Head and Neck Surgery, where parathyroidectomy was recommended. While awaiting the procedure, 30 days later, the patient sustained a fall from her own height with trauma to her right hip. A new X-ray confirmed the presence of a subtrochanteric fracture of the right femur, along with an osteolytic lesion in the greater trochanter of contralateral femur (Fig. 3).

She was admitted through the ER, and the next day, she underwent open reduction and internal fixation of her right femur (Fig. 3). Subsequently, parathyroidectomy was performed uneventfully. She continued with a normal rehabilitation program and follow-up by Nephrology and Endocrinology. After 6 months, new images were obtained showing adequate fixation and consolidation of the fracture without signs of loosening or increased lytic lesions (Fig. 3).

DISCUSSION

Brown tumors constitute a severe and localized manifestation of osteitis fibrosa cystica (OFC). They result from elevated levels of parathyroid hormone (PTH), leading to increased bone resorption rates. This bone is replaced by fibrous tissue and vascular spaces filled with hemosiderin-laden macrophages, giving the lesion its characteristic brown color (2,9).

The cause of these tumors is hyperparathyroidism, which can be categorized as primary when due to hyperactivity of ≥ 1 parathyroid glands, often explained by a benign tumor (adenoma) or glandular hyperplasia; secondary when they are the result of chronic kidney disease (CKD) or vitamin D deficiency (due to reduced calcium absorption leading to increased PTH secretion); and tertiary when they develop in patients with long-standing secondary hyperparathyroidism, characterized by autonomous hypersecretion of PTH even after correction of the underlying cause (10).

Several risk factors are associated with an increased risk of developing these conditions, including age, sex, comorbidities, and certain drugs. Epidemiologically, they are more frequent in elderly patients, particularly those older than 50 years, with peak incidence rates in the 6th and 7th decades of life. This may be explained by age-related renal function impairment, which comprehensively impacts all kidney functions, including the ability to regulate calcium and phosphorus metabolism (11).

A study by Jat et al. (2016) stated that the prevalence of OFC in CKD was 32 %. Some studies have suggested that PTH production and other factors, such as activation of the renin-angiotensin-aldosterone system, cytokine production, and increased growth factor expression may play a role in the pathogenesis of these conditions (12).

Core needle biopsy is the gold standard for diagnosing brown tumors, in which the typical histological finding is clustered osteoclasts on a hemorrhagic fibrotic background (13). Diagnosis is crucial, as differential diagnoses include giant cell tumor, giant cell reparative granuloma, or aneurysmal bone cyst, each with a different prognosis and treatment plan (13).

The etiology of hyperparathyroidism should always be established to define the best therapeutic plan. Parathyroidectomy is considered the gold standard to control primary cases. However, hypocalcemia is a common postoperative complication. Sometimes, it occurs rapidly, profoundly, and lasts more than 4 days, and is associated with hypophosphatemia and hypomagnesemia, a presentation known as hungry bone syndrome (14).

As an alternative to reduce the incidence of the post-parathyroidectomy hungry bone syndrome, the use of bisphosphonates prior to surgery has been proposed. This intervention appears to reduce bone remodeling and attenuate hypocalcemia. Observational descriptive studies have been conducted with preoperative IV zoledronic acid, showing that it significantly reduces the need for IV calcium therapy and the length of postoperative hospital stay, making it a promising option to reduce the rate of hungry bone syndrome in patients with primary hyperparathyroidism (14). Additionally, in 2021, Pal et al. conducted a meta-analysis of observational descriptive studies, finding that preoperative zoledronic acid may be a viable and cost-effective option for reducing hungry bone syndrome in patients with primary hyperparathyroidism, potentially reducing the risk by up to 88 % (15).

However, since the focus of this article is patients with secondary hyperparathyroidism due to chronic kidney disease, it is noted that zoledronic acid is contraindicated in patients with this condition. The use of a single preoperative dose of denosumab is proposed as a great alternative; however, further studies are needed to explore this option (15).

In this article, 3 cases documented in 2023 at a referral hospital in southwestern Colombia were presented, where, in 2 of them, the cardinal presentation that led to the diagnosis of hyperparathyroidism was the presence of a pathological fracture, and in another, an osteolytic lesion was identified at the clinical follow-up, which led to a pathological fracture while awaiting parathyroidectomy. The aim is to emphasize

the importance of this disease, recognize that in some countries, follow-up of CKD patients is not exclusively performed by nephrologists due to socioeconomic factors, which involves a whole group of primary care physicians. The importance of systematically evaluating diagnostic images and suspecting brown tumors in patients presenting with musculoskeletal disease with a history of chronic kidney disease is highlighted to increase prevention, diagnosis, and treatment of hyperparathyroidism in early stages, thereby reducing the incidence of pathological fractures and associated morbidity.

CONCLUSIONS

Brown tumors are a rare clinical sign of prolonged hyperparathyroidism. Despite their potential consequences, this condition is not well-known due to its rare prevalence and clinical variability. Therefore, it is suggested that patients with chronic kidney disease should be evaluated for associated bone abnormalities. Management should be led by a nephrologist; however, in developing countries, the availability of specialists is limited. Thus, it is important to raise awareness among primary care physicians about the thorough investigation of this condition in at-risk populations.

Treatment involves addressing the underlying cause through parathyroidectomy, though this procedure carries significant risks, including the potential for developing hungry bone syndrome. The use of bisphosphonates in the perioperative period has been described, but the evidence is limited and mostly focused on primary hyperparathyroidism. We hope this article encourages further research, particularly in the study of drugs approved for patients with chronic kidney disease.

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Case Report

Bilateral osteonecrosis of the external auditory canal in a patient on bisphosphonates

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Abstract

Introduction: osteonecrosis of the external auditory canal (OEAC) is a rare and poorly recognized skeletal complication of antiresorptive therapy.

Case report: we present the case of a 57-year-old woman with osteoporosis on a 4-year regimen with alendronate. She was referred to an otolaryngologist for the removal of a cerumen plug in her left ear. Otoscopy revealed ulcerated and painless regions on the floor of both external auditory canals, which were consistent with osteonecrosis.

Discussion: although OEAC is an uncommon skeletal complication of antiresorptive use, the development of localized ear symptoms should alert physicians on this rare clinical entity, prompting them to request an otolaryngological evaluation for early diagnosis and treatment.

Keywords:
Bisphosphonates.
Osteonecrosis of the external auditory canal.

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INTRODUCTION

Osteonecrosis of the jaw (ONJ) is a rare but well-known complication (1/1500-1/100,000 patients per year) in patients on oral bisphosphonates for osteoporosis (1). Its development is associated with oral health status, dental trauma due to dentoalveolar manipulation, and possibly decreased bone turnover and as a consequence of the antiangiogenic effects of bisphosphonates. However, osteonecrosis of the external auditory canal (OEAC) is a similarly rare but less well-known complication of treatment with these drugs (2). Although in 2017, the UK Medicines and Healthcare products Regulatory Agency (MHRA) recognized this disorder as a complication associated with bisphosphonates and denosumab, there is still very little awareness or knowledge surrounding OEAC among health care professionals (3). Therefore, we describe the case of a 57-year-old woman with osteoporosis on a 4-year regimen with alendronate who developed bilateral osteonecrosis of the external auditory canal.

CASE REPORT

A 57-year-old woman was referred to our clinic after experiencing a vertebral fracture from a fall while climbing down the stairs. She smoked around 20 cigarettes a day and drank about 40 g of alcohol daily. Her past medical history included bronchial asthma since childhood, adjustment disorder, early non-surgical menopause at age 42, and traumatic fractures of the right tibial plateau and distal fibula. At that time, she was on duloxetine, mirtazapine, and inhaled bronchodilators (beclomethasone/formoterol/glycopyrronium).

Physical examination revealed a BMI of 17.1 kg/m^2 with slight dorsal kyphosis, but no other significant findings. Complete blood count, ESR, routine biochemistry, including calcium, phosphate, and magnesium levels, proteinogram, TSH, and urinalysis all turned out normal. Levels of 25-hydroxyvitamin D (25[OH]D) were low (5 ng/mL) and PTH was slightly elevated (66 pg/mL; normal range [N]: 15-65 pg/mL), while the N-terminal propeptide of type 1 procollagen (P1NP) was slightly increased (90.3 ng/mL; N: 22-60 ng/ml) and the carboxy-terminal telopeptide of type 1 collagen (CTX) was at the high end of the normal range (0.400 ng/mL; N: 0.132-0.410 ng/mL).

Imaging modalities (dorsolumbar X-ray and lumbar-sacral CT) showed an acute fracture of L3 (height loss of the superior endplate < 25 %) and a chronic fracture of L1 (height loss of 30 %). Bone densitometry revealed values consistent with osteopenia in the lumbar spine (T-2.0) and total hip (T-2.2), femoral neck osteoporosis (T-2.5), and a degraded trabecular bone score (TBS, 1.024). Consequently, treatment with alendronate and calcifediol was initiated and was well tolerated.

Four years later, she was referred by her primary care physician to the Otolaryngology Department for the removal of a cerumen plug in her left ear. After the removal of bilateral cerumen plugs impacted at the floor of the external auditory canal (EAC), otomicroscopy revealed osteonecrosis-consistent ulcerated and painless regions in the floor of both EACs. The computed tomography (CT) of the temporal bones (Fig. 1) revealed the presence of mild soft tissue thickening in the walls of both EACs—particularly in the external and middle thirds—associated with small bone erosions in the anterior wall and floor of both EACs, more evident in the left ear, consistent with the clin-

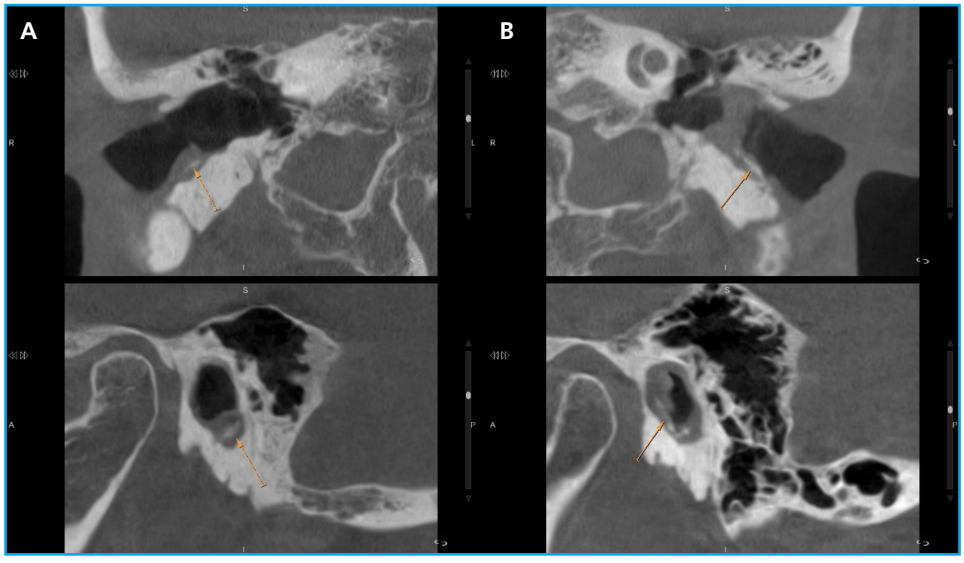

Figure 1. Cone beam computed tomography (CBCT). Coronal and sagittal reconstructions of both external auditory canals (EACs). Moderate stenosis of both external auditory canals (A: right; B: left) due to circumferential soft tissue (likely necrotic skin) and within this, fragmentation and bone sequestra (orange arrows) of the bony cortex. Findings are more prominent on the left side.

ical suspicion of external auditory canal osteonecrosis. The patient had no previous history of treatment with systemic corticosteroids or local radiotherapy, nor any history of malignancy or diabetes. Routine biochemical data were normal. The concentration of 25(OH)D had increased (28 ng/mL) and the markers of bone remodeling had decreased significantly (P1NP: 43.8 ng/mL; CTX: 0.198 ng/mL). Alendronate was discontinued and treatment with teriparatide was initiated. Lesions did not progress at the 2-year follow-up, and the recurrent formation of wax plugs in the necrotic area persisted without complete healing but with clear improvement.

DISCUSSION

Osteonecrosis of the EAC (OEAC) is a rare skeletal complication associated with the use of antiresorptive drugs (2,3). It was first described in 2006 by Polizzotto et al. (4) in a patient with multiple myeloma treated with intravenous bisphosphonates. Since then, around 40 cases have been reported in the literature (3). It is characterized by the appearance of a circumscribed, painless ulcerated area, mainly on the floor of the EAC (2). Some patients may present with otorrhea, otalgia, or recurrent infections, and in advanced stages, facial paresis, hearing loss, and possible involvement of the mastoid and temporomandibular joint. OEAC is a poorly recognized clinical diagnosis among specialists, even otolaryngologists. Additionally, it can be confused with other conditions, such as EAC cholesteatoma or malignant external otitis (2). Similar clinical findings have been made with other antiresorptives, such as denosumab, and with other drugs, such as sorafenib, sunitinib, or bevacizumab, leading some authors to prefer the term drug-related EAC osteonecrosis to describe this condition (3). As with ONJ, OEAC is typically defined as the presence of exposed bone in the EAC for more than 8 weeks in the absence of prior local radiotherapy and after excluding the presence of cholesteatoma or metastasis (5).

According to the literature, the published cases predominantly involve patients diagnosed with osteoporosis (65 %) and, less frequently, patients with malignant neoplasms (35 %) who had undergone prior chemotherapy (3). In the systematic review published by López-Simón et al. (2), the most common presentation was an overinfected ulcer with unilateral bone exposure. Bilateral involvement occurred in about one-third of cases, as in our patient. The initial site of onset was the floor of the auditory canal. Regarding accompanying symptoms, slightly more than one-third of the patients sought medical attention for the onset or exacerbation of a wax plug, while the remaining patients reported chronic otalgia and otorrhea. In some cases, the patient may be asymptomatic or may more easily form wax plugs, as it happened in our case, where the lesion was detected after cerumen removal.

Although the etiopathogenesis of the disease is not fully understood, it is thought that, as it happens with ONJ, local inflammation and infection phenomena, and the inhibition of bone remodeling and angiogenesis, are involved (3,4). In addition to antiresorptive and antiangiogenic therapy, corticosteroids, chemotherapy, minor trauma caused by cotton swabs or fingers, and wax plugs with the formation of wounds in the EAC can be considered risk factors for osteonecrosis. Most cases occurred in patients who had been treated for more than 2 years, and, at least, one-quarter of the patients also had ONJ (3,6).

Imaging modalities are not initially essential to establish the diagnosis. CT of the temporal bone is useful to determine the extent of the lesion, exclude the presence of underlying myeloma, and rule out bone metastases. Technetium-99 bone scintigraphy may be helpful as it can detect subclinical osteonecrosis, confirm the diagnosis of osteomyelitis, and distinguish it from the presence of malignant lesions (2). In cases in which biopsies of the lesions were performed, necrotic and local inflammatory bone changes were observed (7).

As with ONJ, initial treatment is usually conservative and based on the potential discontinuation of the risk drug and treatment with topical corticosteroids and topical or systemic antibiotics. The outcomes have been varied and poorly defined: some cases respond well to conservative therapy, while others require more extensive treatment, such as IV antibiotics, debridement, or surgical resection of the necrotic bone and subsequent reconstruction. However, cases of recurrence after surgical treatment have been reported, so debridement is usually limited to the removal of bone sequestra and sharp edges that may cause repeated direct trauma to the EAC (2,3,7).

In conclusion, OEAC is a very rare and poorly recognized complication of antiresorptive therapy. The development of otorrhea, otalgia, or hearing loss during antiresorptive treatment should alert physicians to this rare clinical entity so that an otolaryngological evaluation can be requested to facilitate early diagnosis and treatment of this condition, preventing the progression of the lesions.

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