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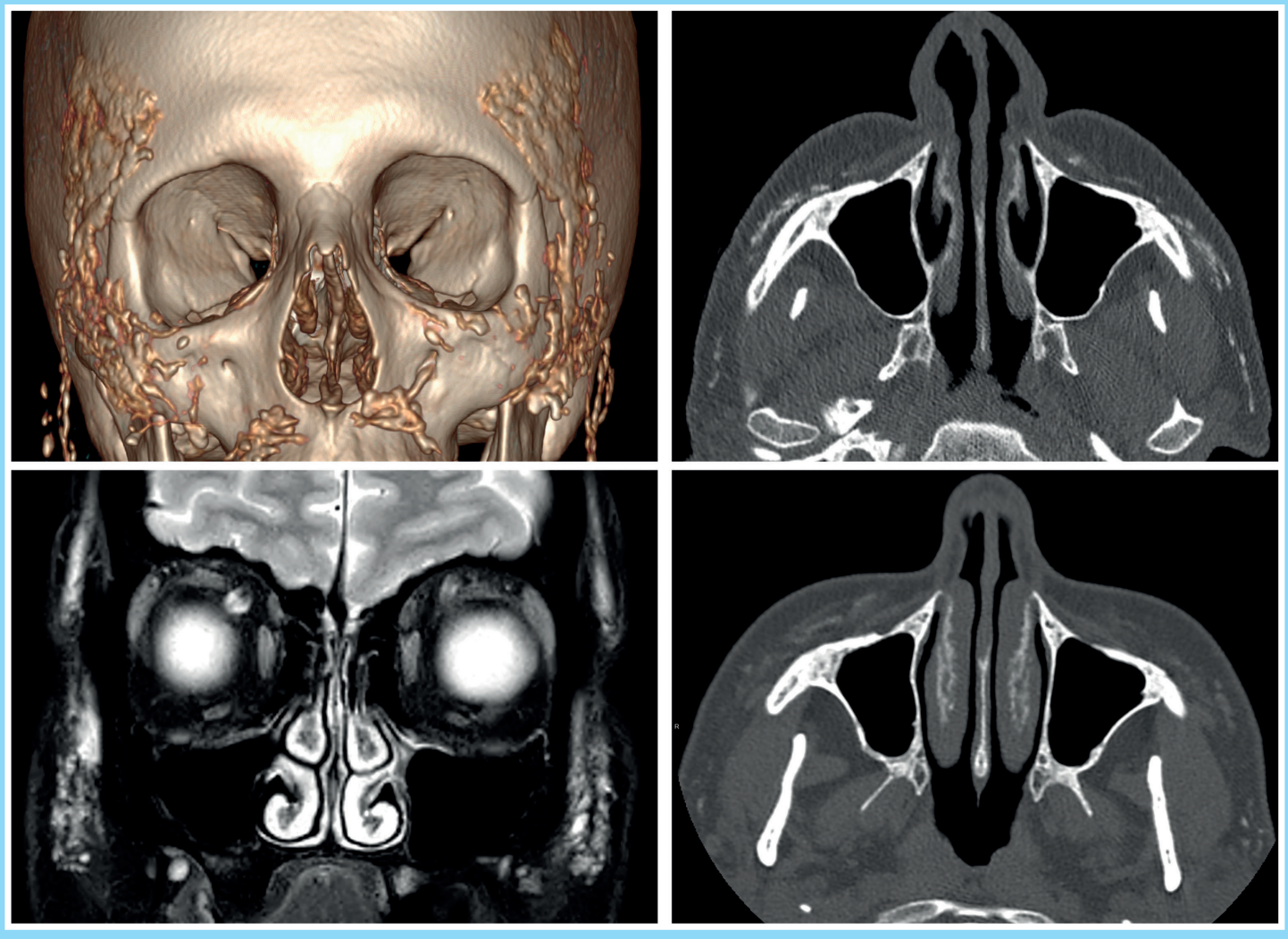

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Summary

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Cover image:

3D reconstruction of a facial CT scan. Coronal image of a T2-weighted fat-saturated magnetic resonance imaging (MRI) sequence. Axial image of a facial CT scan without contrast.

Hospital Universitario Marqués de Valdecilla
Haro Herrera M, Marín Díez E, Olmos Martínez JM. Calcinosis cutis. Osteoporos Metab Miner 2023;15(4):160-163

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Abaloparatide: the new anabolic drug

INTRODUCTION

A new anabolic or bone-forming drug to treat osteoporosis—abaloparatide—will soon become available in Spain. Once launched, there will be 3 anabolic drugs available for prescription: teriparatide, abaloparatide, and romosozumab, although the latter is actually a dual-action drug, that combines anabolic and antiresorptive mechanisms.

As a clinician, and considering the similarities between abaloparatide and teriparatide, I would ask 3 questions: what is the difference in the mechanism of action compared to teriparatide; what are the differences in clinical impact compared to teriparatide; and finally, what is the patient profile that is suitable for treatment with abaloparatide?

WHAT IS THE DIFFERENCE IN THE MECHNISM OF ACTION COMPARED TO TERIPARATIDE?

Answering the first question, teriparatide is the 1-34 fraction of PTH, while abaloparatide is a synthetic analog of PTHrP (PTH related protein). Both molecules act via the PTH type 1 receptor (PTH1R), which has two high-affinity conformations, R0 and RG. Cell signaling response is more prolonged when ligands bind to R0, while the cell response is more transient when they bind to RG. Abaloparatide selectively binds more to the RG conformation of PTH1R than teriparatide (1), and as a result of this more transient cell signaling stimulation, it has been hypothesized that abaloparatide may have a more pronounced net anabolic action (bone formation vs bone resorption) than teriparatide. What is the difference in the mechanism of action compared to teriparatide? (1,2). In this regard, in the ACTIVE trial (Abaloparatide Comparator trial in Vertebral Endpoints), which compared the effects of abaloparatide 80 µg and teriparatide 20 µg, the increase seen in the more robust formation marker, the aminoterminal propeptide of type I procollagen (PINP) was initially similar to that obtained with teriparatide, but after a 3-month administration, this increase was less pronounced compared to teriparatide. At the same time, the resorption marker, the carboxy-terminal telopeptide of type I collagen (CTX), increased more moderately with abaloparatide than with teriparatide across the 18-month study (3).

WHAT ARE THE DIFFERENCES WITH CLINICAL IMPACT COMPARED TO TERIPARATIDE?

When the effects of teriparatide and abaloparatide reducing the risk of fracture and increasing bone mineral density (BMD) are studied in postmenopausal women with osteoporosis, more studies on teriparatide can be found, being particularly prominent here the early trial conducted by Neer et al. (Fracture Prevention trial) and the analyses from the EUROFORS trial (4-7). Therefore, in the study of the effect of teriparatide on the incidence of fractures in postmenopausal women with prior vertebral fractures, a significant reduction of in new vertebral and non-vertebral fractures compared with placebo was demonstrated over a mean 19 months. Teriparatide 20 µg reduced the risk of vertebral fractures by 65 % and the risk of fragility-related non-vertebral fractures by 53 %, becoming the protective effect of teriparatide vs non-vertebral fractures evident after 9 to 12 months. In this study, a reduced risk of hip fracture was not reported, possibly due to the low number of hip fractures reported in both arms of the trial (4). However, a subsequent meta-analysis that included 23 randomized controlled trials on teriparatide 20 µg demonstrated a 56 % reduction in the risk of hip fracture after a mean course of 18 months (8).

The ACTIVE trial aimed to primarily assess the effect of abaloparatide 80 µg on the reduction of new vertebral fractures compared with placebo. Additionally, its impact on reducing non-vertebral, clinical, and major osteoporotic fractures was analyzed. Teriparatide was also included as a comparator (open-label). Abaloparatide significantly reduced the

development of vertebral, non-vertebral, and major osteoporotic fractures compared with placebo over the 18-month study period. The risk of vertebral fractures was reduced by 86 %, while the risk of non-vertebral fractures was reduced by 43 % with abaloparatide vs placebo. When its effects were compared with teriparatide in reducing new fractures, abaloparatide was similar to teriparatide in reducing the risk of vertebral fracture and superior to teriparatide in reducing major osteoporotic fractures. An interesting result to highlight from the study was that abaloparatide showed an earlier reduction in the risk of non-vertebral and major osteoporotic fractures vs placebo than teriparatide. While abaloparatide significantly reduced non-vertebral fractures vs placebo, this reduction was not significant for teriparatide vs placebo in the ACTIVE trial; however, there were not significant differences when abaloparatide and teriparatide were compared. In this regard, the authors comment that the populations of the pivotal studies of both drugs were different, as in the teriparatide trial all patients had, at least, one prevalent vertebral fracture, whereas in the ACTIVE trial only about 25%, which is why these results should be interpreted with caution (3). In fact, a real-world evidence study that compared the efficacy profile of abaloparatide with teriparatide in women with osteoporosis proved that after 18-month of treatment, both anabolic drugs were similar preventing non-vertebral fractures, with abaloparatide also being associated with a significant 22 % reduction in the risk of hip fracture (9). Considering the hip fractures sustained during treatment with abaloparatide and teriparatide in the ACTIVE trial, we should mention that only two cases were found, both in the placebo group (3). A meta-analysis that examined the efficacy profile of all drugs approved to treat postmenopausal osteoporosis in reducing fractures highlighted the effectiveness of both anabolic drugs in preventing vertebral and non-vertebral fractures, with no evidence for hip fracture reduction (10).

When analyzing changes in BMD induced by teriparatide and abaloparatide in the two pivotal studies, the Fracture prevention trial and the ACTIVE trial, with different populations, reported a significant and similar increase in BMD in the lumbar spine of 9 % and 10.4 % for teriparatide and abaloparatide, respectively, compared with placebo (3,4). At the femoral neck increases compared with placebo were 3 % for teriparatide and 4 % for abaloparatide. When the changes in BMD induced by teriparatide and abaloparatide were compared in the ACTIVE trial at 18 months of the study, the increased BMD in the lumbar spine was practically identical for both drugs. However, the femoral neck and total hip BMD increase was significantly higher for abaloparatide at 6, 12, and 18 months (3). Volumetric hip density measurement using 3D-DXA in a post-hoc analysis of the ACTIVE trial showed that only abaloparatide increased cortical density, while both abaloparatide and teriparatide increased trabecular density at 18 months (11).

The ACTIVE trial analyzed the safety profile, and adverse events of abaloparatide and teriparatide. Discontinuation of the study due to adverse events was more common in the abaloparatide group (9.9 %) than in the teriparatide group (6.8 %). Abaloparatide induced hypercalcemia less frequently, particularly when the sample was obtained 4 hours after the injection. Perhaps an adverse event we should mention associated with abaloparatide was a higher frequency of palpitations, with other adverse events being balanced between both treatment groups (3). It is worth noting that abaloparatide has the same administration contraindications as teriparatide.

Sequential therapy was also included in the development of abaloparatide with an extension of the ACTIVE trial, in which alendronate was administered for 24 months after 18 months of abaloparatide or placebo. With the abaloparatide/alendronate sequence, the risk of vertebral, non-vertebral, clinical, and major osteoporotic fractures was reduced, along with greater gains in BMD compared to placebo/alendronate (12).

Overall, and trying to answer the question of what are the differences between abaloparatide and teriparatide with clinical impact, both anabolic agents are effective in reducing vertebral and non-vertebral fractures in postmenopausal women with osteoporosis. Perhaps abaloparatide has a faster action in reducing non-vertebral and major osteoporotic fractures and a more favourable effect on the cortical bone of the hip, which could translate into a reduction in fractures at this level, although this aspect needs to be confirmed.

PROFILE OF PATIENTS ELIGIBLE FOR ABALOPARATIDE

The profile of patients who would be suitable for treatment with abaloparatide should be based on the recommendations for the administration of anabolic drugs in postmenopausal osteoporosis according to the clinical practice guidelines (13,14). The indication for abaloparatide would therefore be in women at very high risk of fracture. González-Macías et al, in their thoughtful special article in this volume of *Journal of Osteoporosis and Mineral Metabolism (Revista de Osteoporosis y Metabolismo Mineral)* (15), highlight the lack of homogeneity of this concept. There is a significant variability in the factors included in the classification of very high risk of fracture: T-score ranging from ≤ -2.5 to ≤ -3.5; a history of either a single vertebral fracture or multiple vertebral fractures and/or major osteoporotic fractures and/or hip fractures; a very high fracture probability according to FRAX; and in numerous guidelines, the time elapsed after the fracture, which ranges from 12 months to 3 years. Therefore, I will focus on the indication for anabolic drugs based on the

SEIOMM guidelines: "very high risk corresponds to women with a) two or more vertebral fractures or an equivalent situation (such as vertebral and hip fracture); b) very low BMD (T < -3.5), or c) vertebral or hip fracture, along with a T-score < -3.0" (16). While it is true that under this definition of very high risk, teriparatide and romosozumab are recommended in all recent guidelines, including that of SEIOMM, abaloparatide is also included at the same level in guidelines from countries where abaloparatide was available, such as the United States (13,14). We should mention that abaloparatide was not available in European countries when most of the latest clinical guidelines were published (16,17).

Some clinical practice guidelines, such as those published by the Endocrine Society recommend teriparatide or abaloparatide for postmenopausal women at a very high risk of fracture "such as those with severe or multiple vertebral fractures," differentiating their indication from romosozumab, which is recommended "in women with a low T-score < -2.5 and fractures, or multiple vertebral fractures" (14). Similarly, the Swiss Association against Osteoporosis guidelines from 2020 recommend teriparatide for postmenopausal women with prevalent vertebral fractures and a very high risk of fracture (17). Cosman et al., in an article on the selection of the most ideal anabolic agent according to the characteristics of the patient, highlight the suitability of abaloparatide, closely followed by teriparatide, in patients with a very high risk of vertebral fracture on the basis of prevalent vertebral fract (particularly multiple, severe, or recent), or very low BMD in the spine and/or a severely degraded trabecular bone score (TBS). For patients with a very high risk of non-vertebral fractures, especially those with hip fractures or other major osteoporotic fractures and/or very low BMD at the hip, Cosman favors romosozumab as the first-line therapy, abaloparatide as the second option, and teriparatide as the third option in this scenario (18).

Specifically, the patient profile that would benefit from treatment with abaloparatide would include postmenopausal women at very high risk of fracture, particularly vertebral fracture, where reducing the risk of vertebral and non-vertebral fracture is required. In addition, abaloparatide could be effective in reducing the risk of hip fracture and may be superior to teriparatide when very rapid action is desired to reduce the risk of major osteoporotic fractures. These aspects, particularly its possible effect on reducing the risk of hip fracture, require further detailed analy

CONCLUSION

Abaloparatide is a new anabolic option for postmenopausal women at very high risk of fracture, particularly vertebral fracture. Abaloparatide binds more selectively to the RG conformation of PTH1R than teriparatide, resulting in a more transient cell signalling response and a greater net anabolic effect. The ACTIVE trial and its extension are the most relevant studies of abaloparatide, complemented by a study with real-life data. Together, they show similar efficacy of abaloparatide to teriparatide in reducing the risk of vertebral and non-vertebral fractures compared with placebo, with greater increases in BMD at the femoral neck and total hip at the expense of cortical bone. Based on the available data, the profile of the patient who would benefit from treatment with abaloparatide would be a postmenopausal woman at very high risk of fracture, particularly vertebral fracture. Possibly, abaloparatide reduces the risk of major osteoporotic fractures more rapidly than teriparatide and perhaps shows efficacy in reducing hip fractures due to its effect on cortical bone, but these features need to be further analysed.

Conflicts of interest: Núria Guañabens received speaker and consultant fees, and travel allowances from Amgen, Eli Lilly, Gedeon-Richter, Theramex, and UCB.

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Original

Impact of fragility fractures in postmenopausal Spanish women with osteoporosis

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Abstract

Objective: given the impact of fragility fractures and their consequences on the lives of women with postmenopausal osteoporosis (PMO), the objective of this study is to describe and analyze the impact of this kind of fractures on this population.

Materials and methods: a survey was conducted among postmenopausal women with fragility fractures in a cross-sectional observational design. Sociodemographic variables, fracture impact (need for care, work productivity), and data on health-related quality of life (HRQoL, assessed using the QUALEFFO-31 questionnaire), and willingness to pay (WTP) to regain HRQoL were collected.

Results: a total of 120 women participated, with a mean age of 62 ± 7 years. The most frequent fractures described were distal radius fractures (29.9 %), followed by vertebral fractures (21.3 %). A total of 53.3 % required care during their recovery (76.5 %, informal; 24.9 %, formal), and 4.2 % had to be admitted to a health care or nursing home. Among those who were working when the fracture occurred (62.5 %), 56 % had their working life affected (69.3 %, temporary disability; 17.3 %, permanent disability; 10.7 %, reduced working hours; 10.7 %, quit their jobs; 5.3 %, leave of absence; and 3.6 %, early retirement). The impact of the fracture was primarily due to pain (71.7 %), difficulty performing activities of daily living (48.3 %), mobility problems (46.7 %), and emotional state (41.7 %). The highest WTP was offered to regain the ability to perform activities of daily living and improve the emotional state. The overall QUALEFFO-31 score (0-100) was 49.9 ± 10.8 (mental function, 68.3 ± 7.3; pain, 56 ± 22.6; physical function, 39.3 ± 15.5).

Conclusions: fragility fractures play a significant role on the quality of life of women with PMO. It is of paramount importance to value the aspects that concern them the most to optimize their management.

Keywords:
Fragility fracture. Postmenopausal osteoporosis. Quality of life. Disease burden. Willingness to pay. Intangible costs.

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INTRODUCTION

Back in 2017, a total of 327 600 fragility fractures occurred in Spain, 260 000 of them in women (1). Fragility fractures are defined as those due to low-impact events, such as falling from a standing height, and are the main consequence of osteoporosis, a disease affecting 22.5 % of Spanish women older than 50 (2), a percentage that goes up to 40 % in women aged 70 to 80 years (3).

The risk of experiencing this type of fracture after menopause ranges from 39 % to 53 % (4). Fragility fractures lead to over-use of health care resources because, in some cases, they require hospitalization, and their complications can increase the overall risk of mortality (5-7). Therefore, according to some estimates, they represent the 4th chronic disease causing the greatest impact (disability-adjusted life years), followed by ischemic heart disease, dementia, and lung cancer, thus leading chronic obstructive pulmonary disease (COPD), stroke, and rheumatoid arthritis (1,8). Also, an initial fracture increases the risk of further short-term fractures (1 year) by up to 5 times (9) and can trigger a cycle of health care dependence, increased cost for the health care system, and a worse health-related quality of life (HRQoL) (1). Still, it is estimated that approximately 3 out of every 4 patients do not receive treatment to prevent new fragility fractures (1,2).

The risk of suffering a new fragility fracture is significantly stressful for individuals affected by it. Among the main concerns are the fear of falling and fracturing, the inability to perform household tasks properly, or groom themselves without assistance, or the uncertainty surrounding the future (10-12). Long-term loss of independence is another major concern, especially in the case of hip fractures sustained at advanced ages (13,14).

The present study is based on a survey targeting Spanish women with PMO who sustained a fragility fracture in the past in an effort to provide information on its impact on activities of daily living. Specifically, we intend to describe a) sociodemographic and clinical aspects of women with PMO and fractures; b) dependence and time spent on care; c) work impact; d) the effect of fractures in different areas of life; e) willingness to pay to regain the pre-fracture situation; and f) HRQoL.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

This was an observational cross-sectional study based on an online questionnaire aimed at adult women with PMO who had sustained, at least, 1 OP-related fracture (spontaneous or after a fall) and were Spanish residents (inclusion criteria). Candidates were invited to participate via email (through GfK, Growth from Knowledge), in an online survey designed for this purpose by the research team. Participants agreed to collaborate voluntarily without receiving any financial compensation from the study sponsor, or research team.

Based on the number of women older than 50 years in Spain (n = 10,184,457) (15), the prevalence of osteoporosis in this group (2), and the risk of fracture (3), the study population was estimated at around 1,221,340. Considering that most responses to the survey would be measured as a proportion, the sample size calculation applied the proportion estimation formula assuming maximum indeterminacy (16), with a 95 % confidence interval and a precision error of 9 %. As a result, a sample size of 120 participants was obtained. The survey was closed when the estimated sample size was reached.

THE QUESTIONNAIRE

The questionnaire was developed specifically for the study. A scientific committee including 10 health care professionals, a health economics specialist, a representative from the Spanish Association for Osteoporosis and Arthritis (AECOSAR), and an expert female patient, reviewed the questionnaire to determine the appropriateness of the questions and their comprehensibility. The study was evaluated and approved by the Drug Research Ethics Committee (DREC) of Hospital Universitario Puerta de Hierro Majadahonda (Madrid, Spain).

The questionnaire included a total of 33 questions distributed across 6 sections (supplementary data): a) sociodemographic variables (age, autonomous community of residence, family situation/living arrangements, membership in any OP-related patient association); b) clinical data (age at menopause, location, number, and year of fragility fractures, most affected fracture, comorbidities); c) caregiver-related data (after the fracture: need for admission to recovery centers and duration, need for a caregiver, hours/week of caregiver dedication); d) productivity-related data (current employment status, employment status before the fracture, impact of the fracture on work activity); e) impact of the fracture on activities of daily living (compared to the situation prior to the fracture: impact on activities of daily living, mobility, pain, leisure activities, family relationships, intimate life, and psychological/emotional well-being); and f) data related to willingness to pay (participants' willingness to pay to return to the pre-fracture state for each of the affected areas. Response ranges: < € 500, € 501-€ 1000, € 1001-€ 1500, € 1501-€ 2000, € 2001-€ 2500, € 2501-€ 3000, > € 3000). At the end of the survey, the specific QUALEFFO-31 questionnaire (17), validated in Spanish (18), was included to assess quality of life in women with osteoporosis. This questionnaire is divided into 3 different domains: pain, physical function, and mental function, with a total of 100 points possible in each domain and overall, indicating the highest scores a worse quality of life.

STATISTICAL ANALYSIS

Data analysis was conducted using the STATA v.14 statistical software package. For the descriptive analysis of the sample, relative and absolute frequencies were calculated for qualitative variables, while central tendency and dispersion statistics (mean, standard deviation [SD], minimum, maximum, and quartiles) were calculated for quantitative variables. To estimate the mean willingness to pay to improve several aspects of quality of life, only the responses of patients who had an impact in each area were considered. To do this, responses on monetary ranges were replaced by the midpoint of the interval, and a 50 % correction was applied (improvement for other reasons).

RESULTS

SOCIODEMOGRAPHIC CHARACTERISTICS

The study included a total of 120 participants, all of whom were women with PMO with > 1 previous fragility fractures. The patients' mean age was 62 years (SD, 7.1; range, 49-84). Participants were recruited from 16 Spanish autonomous communities, with the following distribution: Valencian Community (24.2 %), Canary Islands (16.6 %), Extremadura (11.6 %), Andalusia (10.8 %), Aragon (5.8 %), Balearic Islands (5 %), Asturias (4.2 %), Madrid (4.2 %), Murcia (2.5 %), Basque Country (2.5 %), La Rioja (2.5 %), Navarra (2.5 %), Castilla-La Mancha (2.5 %), Galicia (1.6 %), Cataluña (1.6 %), Castilla y León (1.6 %). A total of 74 % of participants (n = 89) were living with someone else, while the remaining 26 % (n = 31) lived alone. Most participants (97.5 %, n = 117) were not members of any patient association related to OP.

CLINICAL DATA

Menopause mean age was 49 years (SD, 5.2; range, 34-65). The mean number of fragility fractures sustained by the participants was 1.6 (SD, 1.2; range, 1-8), with 36.7 % of them having sustained 2 or more fractures. Among the different types of fractures reported in the survey, the most common ones were distal radius fractures (29.9 %), followed by vertebral fractures (21.3 %), proximal humerus fractures (7.6 %), and hip fractures (6.1 %) (Fig. 1). Accordingly, the type of fracture that had impacted the participants' activities of daily living more significantly was distal radius fractures (32 %), followed by vertebral fractures (18 %), proximal humerus fractures (11 %), and hip fractures (7 %). The mean time elapsed since the first fracture occurred was 7.5 years (SD, 5.8), and 5.5 years (SD, 3.1) since the last one.

In addition to osteoporosis, the most common conditions described among the participants were vision problems (20.8 %) and thyroid gland disorders (20.8 %), followed by early menopause, periods of amenorrhea, and ovariectomy (16.7 %), rheumatoid arthritis (15.8 %), osteoarthritis (14.1 %), COPD (10.8 %), and breast cancer (10 %). Diabetes, cardiopulmonary disease, and balance disorders were present in 6.7 % of the cases. Chronic kidney disease (3.3 %), peripheral neuropathy (1.7 %), and, with only 1 case (0.8 %), celiac disease, cerebrovascular disease, Parkinson's disease, and inflammatory bowel disease were among the least common diagnoses of all. Nearly 22.5 % of the patients said they had not been diagnosed of any other diseases and conditions.

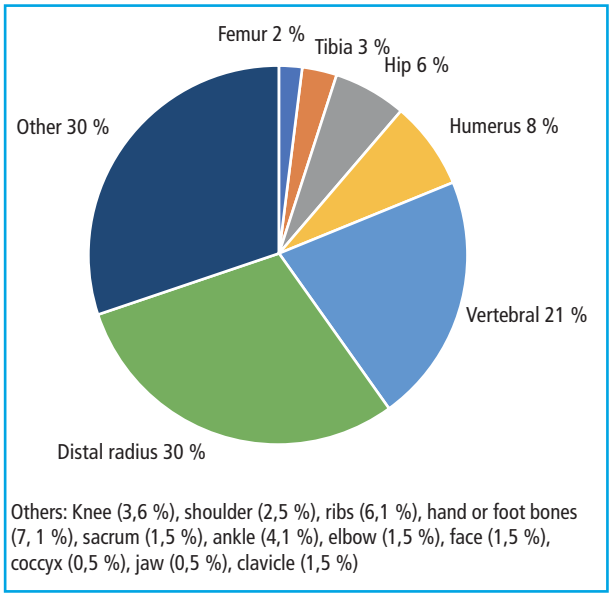

Figure 1. Distribution of participants based on the type of fracture sustained.

IMPACT OF FRACTURES ON THE ACTIVITIES OF DAILY LIVING

Overall, pain was the most common symptom (71.7 %) experienced after the fracture, followed, in almost half of the cases, by difficulties performing activities of daily living (dressing, showering, cleaning, shopping, etc.), and mobility problems (walking or moving inside or outside the house, getting up, bending down or kneeling, using public transportation, etc.), compared to the situation prior to the fracture (Fig. 2A). The same trend was seen when only women who had sustained vertebral fractures were considered (the second most common type of fracture), although in this case, pain affected more than 90 % of the patients. In the case of distal radius fractures (the most common fracture), pain and difficulty performing activities of daily living were also among the most common symptoms of all (55.2 % and 31.5 %), followed, in this case, by an impact on leisure activities (28.9 %).

A total of 41.61 % of the patients (n = 50) reported that fractures had an impact on their emotional life. In the case of women who said that distal radius fractures and vertebral fractures had been the ones that had impacted the activities of daily living more significantly, the percentage with emotional impact was 18.4 % (n = 7) and 40.9 % (n = 9), respectively. Overall, most of them had experienced loss of sleep quality and anxiety. Depression, mood swings, stress, and low self-esteem were among the symptoms also reported by the patients (Fig. 2B).

QUALITY OF LIFE QUESTIONNAIRE

The mean overall score on the QUALEFFO-31 was 49.9 (SD, 10.8; range 33.5-83.2). Figure 3 illustrates the mean overall score, as well as the specific scores for the questionnaire domains for all participants and those with the most common fractures of all (distal radius and vertebral fractures). Overall, a poorer quality of life was seen in the mental function domain (mean, 68.3; SD, 7.3; range, 51.1-84.4), followed by pain (mean, 56; SD, 22.6; range, 20-100) and physical function (mean, 39.9; SD, 15.5; range, 18.9-94.4). The same trend was seen in women who said that distal radius and vertebral fractures were the ones that had the most significant impact on their activities of daily living.

CAREGIVER-RELATED DATA

At the time of the survey, most participants (79.1 %) did not have a caregiver. As a matter of fact, 4.2 % of

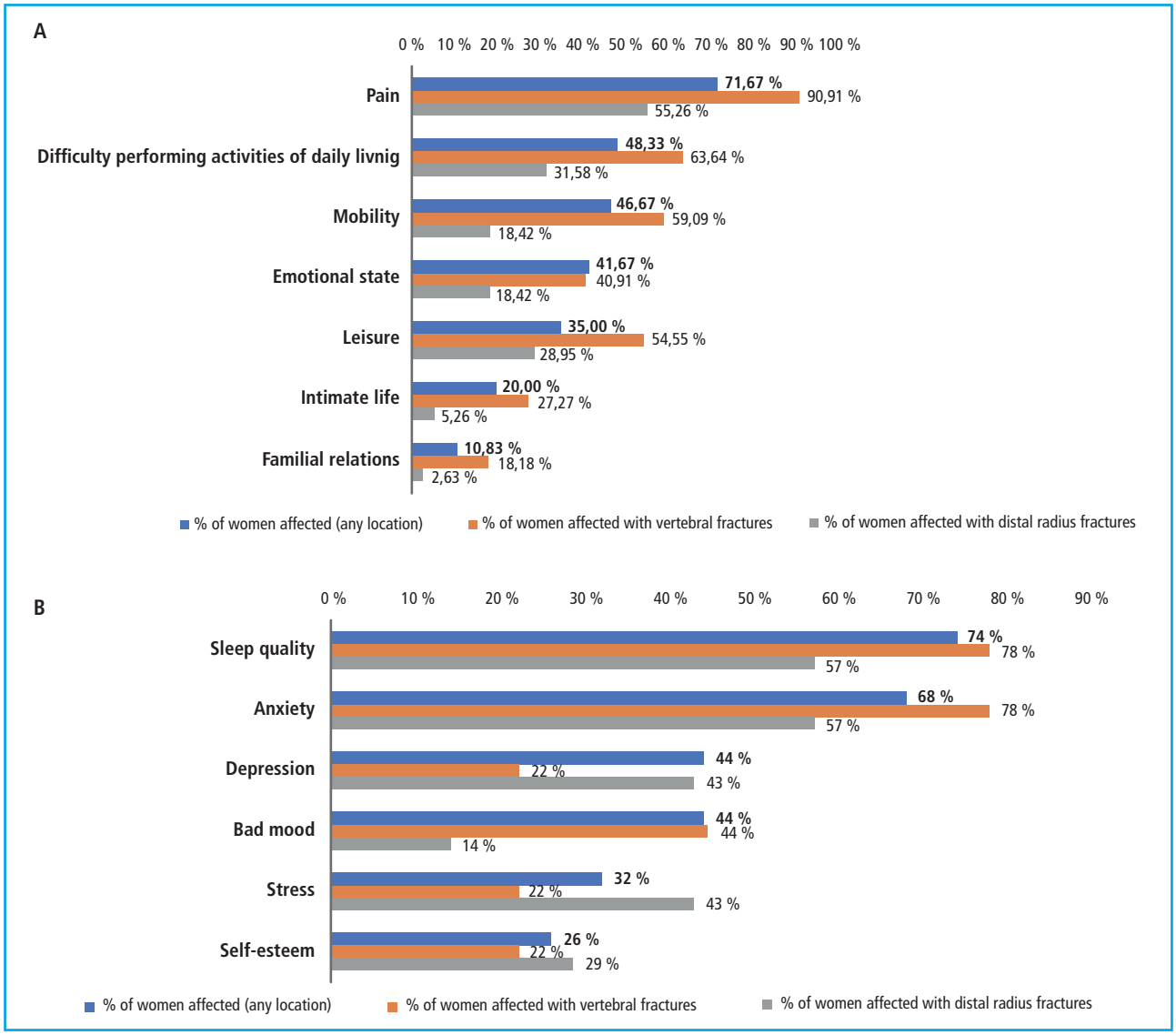

Figure 2. Impact the fracture had on different life domains (A) and type of emotional impact (B).

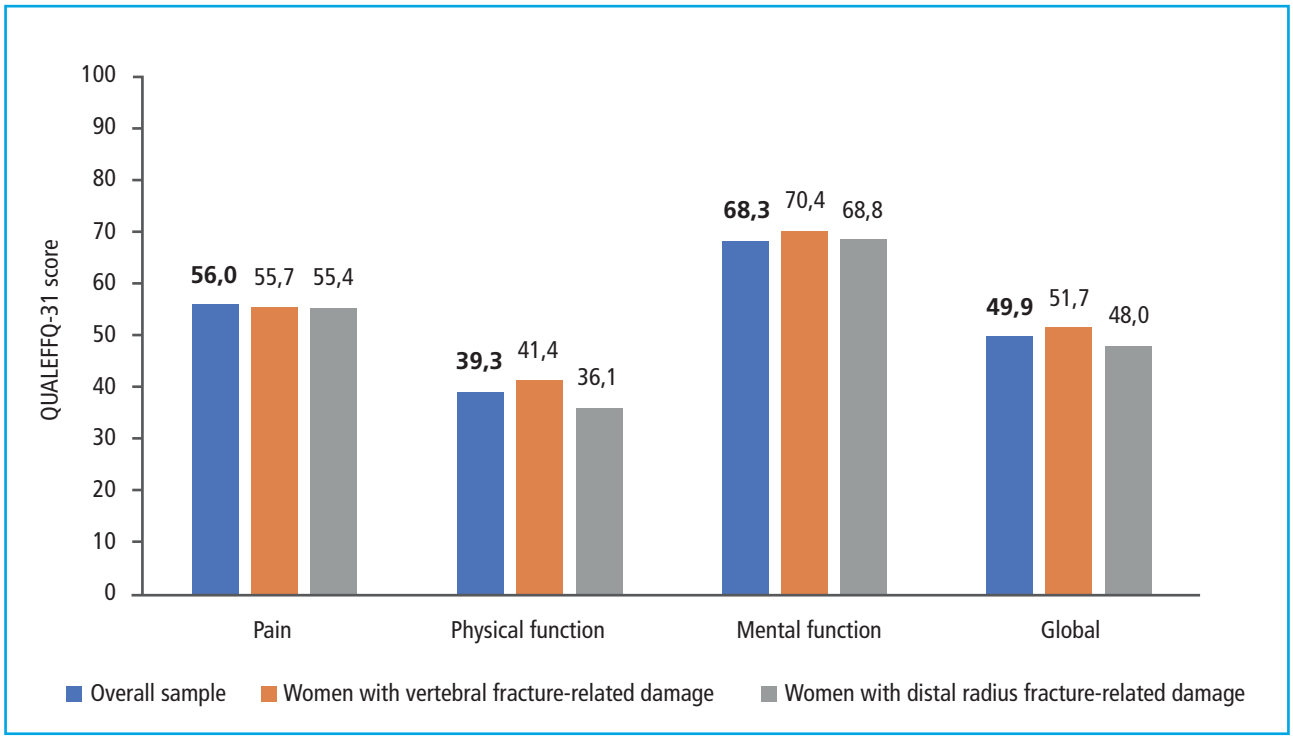

Figure 3. Quality of life reported by patients using the QUALEFFO-31 questionnaire (mean score).

them were in charge of the personal care of another patient. Nearly 15.8 % received care from a family member, and only 1 case (0.8 %) from a professional caregiver.

After sustaining a fragility fracture, 64 of respondents (53.3 %) required professional or family caregiver assistance during their recovery. Among them, 9 patients (14.0 %) had to pay for the caregiver (themselves or their families), 7 (10.9 %) had a home caregiving service provided by the health care system, and 49 (76.5 %) received non-professional care. Additionally, 5 participants (4.1 %) had to be admitted to a center or nursing home for their recovery, with a mean length of stay of 2.8 months (SD, 4).

The mean duration of the care and assistance provided by the caregivers was 8.8 months (SD, 17.7); for private assistance, 19 months (SD, 28.1); for health care assistance, 7.2 months (SD, 13.4); for non-professional care, a mean weekly caregiving time of 30.4 hours (SD, 52.8), 5.8 hours (SD, 6.9), and 21.3 hours (SD, 28.4), respectively.

WORK PRODUCTIVITY-RELATED DATA

A total of 62.5 % (n = 75) of the participants were actively employed at the time of the fracture. Among the working participants, 74.6 % (n = 56) reported that the fracture had affected their work life. Among them, 69.6 % had applied for temporary disability (with a mean duration of 120 days; SD, 117.6). Additionally, 17.8 % had to apply for permanent disability after a mean 23.1 months (SD, 28.4) following the fracture. Nearly 10.7 % had to reduce their working hours (averaging 4.4 hours per day; SD, 2.3 or 336 days on average; SD, 163.4), 10.7 % had to stop working or lost their jobs, 5.3 % had to take days off or leaves of absence (averaging 61.6 days; SD, 57.5), and 3.6 % had to take early retirement after a mean 13.5 months since the fracture occurred (SD, 14.8).

WILLINGNESS TO PAY-RELATED DATA

When participants were asked how much they would be willing to pay to regain their pre-fracture state in different aspects of their daily life, within specified ranges, the highest willingness to pay was observed for the ability to perform activities of daily living and emotional well-being. On the other hand, the lowest willingness to pay was reported for the work situation and family relationships (Table I).

DISCUSSION

This observational study provides valuable information to understand the impact of fragility fractures on the quality of life of women with PMO. Additionally, it provides nov-

Table I. Estimation of willingness to pay in each domain of health-related quality of life under consideration

Setting	% of damage	Mean WTP
Working situation	47 %	€ 379.46
Capacity to perform activities of daily living	48 %	€ 625.00
Same degree of mobility	47 %	€ 598.21
Same degree of pain	72 %	€ 587.21
Leisure activities	35 %	€ 446.43
Familial relations	11 %	€ 432.69
Intimate life	20 %	€ 468.75
Emotional state	42 %	€ 605.00
Overall cost of WTP*	--	€ 1728.13

**Cost weighted based on the number of patients showing damage from each individual setting.*

el data to assess the intangible burden and costs associated with this disease.

The survey results reveal the participation of relatively young women (mean age, 62 years), compared to the population typically observed in the routine clinical practice, where the mean age of women with PMO who have experienced fractures is closer to 75 years (19,20). However, these women had already experienced a mean of 1.6 fragility fractures. This mean age is also consistent with former studies (63 to 65 years) based on surveys targeting women with similar characteristics to assess HRQoL (21,22). The participants' age could explain the percentage and location of the fractures reported, being wrist fractures the most common and hip fractures the less common of all (1). This is likely due to the fact that the incidence of hip fractures increases exponentially with age, ranging from 7 % in women aged 55 to 59 years up to 34 % in those older than 85 years (23).

Fragility fractures not only had a physical impact but also an emotional one. Pain and psychological well-being are 2 dimensions of HRQoL significantly affected, according to the results, which prompts consideration of the appropriate management of the disease. Former studies have identified pain as one of the most affected domains in women with PMO who have sustained fractures (21,24). Additionally, vertebral fractures can cause long-term pain, with some women still experiencing it several years after having sustained their fracture (25). The results of the QUALEFFO-31 questionnaire show a greater dispersion in this area, with some women reaching the maximum possible score (100 points, which is indicative of a worse quality of life). This questionnaire was previously used in a study of Spanish women with PMO (mean age, 59 years) where fragility fractures were not considered (18). Therefore, the scores in all domains were likely lower than those obtained in the present study, being pain the least affected dimension (physical function, 21.6; mental function, 19.8; pain: 10.8) (18). The impact of pain and physical impairment is evident in women who have sustained fragility fractures. However, the mental function domain was the one where the worst quality of life was reported. Consistent with former studies conducted among postmenopausal women with osteoporosis (26), anxiety emerges as a prominent sign of emotional distress. The fear of sustaining yet another bone fracture is one of the main concerns of women who have previously sustained a fragility fracture (27). In this regard, secondary prevention plays a key role where there is large room for improvement, because most individuals with fragility fractures are not assessed or treated to reduce the risk of a second fracture (28,29). Regarding treatment, it has been estimated that only 28 % of Spanish women receive treatment to prevent fractures in the year following the index fracture (2). Also, treatment compliance is not even close to 35 % (30).

The degree of interdependence of individuals who suffer fragility fractures can vary depending on their age and type of fracture sustained. This variation is particularly evident considering that distal radius fractures typically occur around the age of 60, vertebral fractures around the age of 70, and hip fractures around the age of 80. Particularly the latter often require hospitalization and more extensive care (2). We should mention that because of the mean age of the study participants (62 years), hip fractures were underrepresented, and possibly because of this, at the time of the survey (a mean 5.5 years after sustaining the last fracture), most participants did not require a caregiver. However, more than half of them reported needing care during their recovery from the fracture, despite being relatively young women. This is a remarkable finding because it means that regardless of the location where fractures occur, they can lead to a significant degree of interdependence due to limited activities of daily living. Additionally, most care was provided by unpaid caregivers. The informal care required by wom-

en with PMO after sustaining a fragility fracture is one of the hidden burdens of these fractures impacting society (1), which is also evident in our study.

The loss of labor productivity is another social burden associated with fragility fractures that was also explored in the survey. Although these fractures primarily affect elderly individuals, around 20 % of them occur prior to retirement age (31). In our study, more than half of the participants sustained a fragility fracture while still actively working, and the data they provided is particularly valuable to estimate the indirect costs associated with the disease.

We should mention how important functionality was for the study participants, despite having sustained mostly fractures with less associated disability than hip fractures (2). In a hypothetical scenario where those affected could pay to regain their pre-fracture condition, they would pay the highest amount of money to regain their ability to perform activities of daily living. Once again, pain and the emotional state were among the aspects that patients assigned the highest value to. These results are fundamentally relevant to understand which aspects of the lives of women' who sustain fragility fractures are most important to them. Since participants had closed response ranges, the economic value per se should be assessed with caution. However, it can help estimate the intangible cost of the disease conservatively. The WTP to regain different aspects of daily living will depend on the condition under consideration, its consequences, and the characteristics of the individuals sustaining the fracture. Therefore, in a former study of patients with psoriasis where the same response ranges were used, the highest value was assigned to regain the ability to work (€ 843) and family life (€ 843), while the WTP to go back to performing activities of daily living was the lowest of all (€ 535) (30).

The survey has several limitations inherent to its design and the study population. The use of ad-hoc questions in the questionnaire can be a limitation too. Regarding the study population, we should mention that patients belonged to a panel of participants from a company specialized in conducting opinion and market research studies through digital media. Therefore, characteristics such as the mean age and, consequently, the type of fractures sustained may not be representative of the overall population with PMO, as previously mentioned. The impact of fractures may have been underestimated (greater if more hip fractures would have been collected), while the labor impact may have been overestimated (lower if fractures would have occurred after retirement). The participants' high comorbidity could also be partly attributed to the panel's characteristics (women motivated to answer questions on their health status). On the other hand, autonomous communities with large populations, such as Catalonia, Andalusia, and Madrid, were underrepresented. Another limitation associated with the type of study is that data are not supported by any particular physician or health record, which could have led to overestimating some fragility fractures, such as metatarsal fractures, which could have occurred due to causes unrelated to PMO, in addition to the fractures classified as "other" (where the exact location of those classified as femur is also unknown). Additionally, no questions were asked on whether vertebral fractures were clinical or only morphometric, although it is assumed that they were clinical due to the high percentage of individuals who sustained fractures and reported experiencing pain. Finally, the years passed since the last fracture occurred (mean, 5.5 years) could have affected the patients' subjective recall of the most immediate impact of the fracture. Despite these limitations, all the questions in the questionnaire were associated with osteoporosis and its consequences (including a specific HRQoL questionnaire). Also, the data provided are highly valuable when it comes to understanding aspects of daily living most generally affected after sustaining fragility fractures.

This study highlights the significant impact that fragility fractures have on the lives of women with PMO, where pain, the ability to perform activities of daily living, independence, and emotional state are primarily affected. Recognizing the aspects that are more concerning for patients is essential to prevent and optimize the management of fragility fractures. Due to its impact on HRQoL, we should focus our efforts on optimizing the management of PMO, secondary prevention, reducing the risk of sustaining new fractures, and avoiding their consequences.

CONFLICTS OF INTEREST

IE has received fees for presentations and consultancy jobs done for UCB, Amgen, Lilly, Theramex, Grunenthal, and Italfármaco. JRC has received fees as a consultant and/or speaker from Amgen, Gebro, Gedeon-Richter, Grünenthal, Lilly, MSD, UCB, Synthex (J&J), Stryker, and Theramex. FJO and TP declared no conflicts of interest whatsoever. MJM-A has received lecture fees, travel grants, and advisory fees from Stada, Amgen, UCB, Grünenthal, Gedeon Richter, and Rubió. PP has received speaking fees from Amgen, UCB, Lilly, and Kyowa Kirin Farmacéutica. AN has received fees for presentation jobs done for UCB, Amgen, Galapagos, Abbvie, and Lilly; consultancy fees from Abbvie and UCB; and for attending conferences on behalf of UCB, Amgen, Pfizer, and Abbvie. VPdR has received fees from Amgen, UCB, Stada, and Grünenthal. EJ has received consultancy fees from Amgen, AstraZeneca, FAES, Helios-Fresenius, Italfármaco, Lilly, MSD, Mundipharma, Novo Nordisk, UCB, and Viatris; as a clinical researcher, he has received fees from Amgen, Boehringer, AstraZeneca, FAES, Janssen, Lilly, MSD, Novo Nordisk, Pfizer, Sanofi, Shire, and UCB; and as a speaker he has received fees from Amgen, Asofarma, Astellas, AstraZeneca, Bayer, Boehringuer, BMS, FAES, Lilly, MSD, Mundipharma, Novo Nordisk, Technofarma, UCB, and Viatris. MGG has received presentation and consultancy fees from UCB, consultancy fees from Astellas, Vifor, An-

gelini, and Janssen, and through a competitive grant from MSD. JV declares that UCB and AMGEN collaborate in supporting AECOSAR patient educational programs, an association I am the president of. SM is an employee of UCB. ICT is an employee of Amgen. LB-P and SA are both employees of Outcomes'10, an independent research company that has received funding from UCB for coordinating this study.

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Review

Function of sex hormones in bone homeostasis and their role in the development of male osteoporosis: a narrative review

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Abstract

Bone is a dynamic tissue that undergoes constant adaptation throughout the life of vertebrates to achieve size, shape, preserve the structural integrity of the skeleton, and regulate mineral homeostasis. Bone growth during childhood is crucial to achieve height and resistance to fractures later in life. Sex hormones play a key role in bone remodeling in men and women alike, and changes to hormonal profiles can trigger bone metabolism-related diseases. In women, estrogen deficiency during menopause is one of the leading causes of osteoporosis, while in men, androgens can have an impact on bone health by binding directly to androgen receptors or indirectly to estrogen receptors.

This review explores the role and effects of sex hormones on bone metabolism, the signaling pathways involved, and the effects that can trigger diseases such as osteoporosis.

Keywords: Male osteoporosis. Androgens. Estrogens. Testosterone.

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INTRODUCTION

Osteoporosis (OP) is one of the most common metabolic diseases across the world. OP is characterized by the loss of bone mass and the deterioration of bone microarchitecture, predisposing patients to sustaining fragility fractures (1). OP is considered a subclinical condition until it becomes complicated with a fracture, which poses a medical, personal, and high socio-economic burden, and the use of several resources required for the management of affected individuals (2,3). OP is often considered a condition that affects postmenopausal women. However, in recent years, it has been reported that one-third of all hip fractures sustained occur in men, and the incidence of vertebral fractures can exceed more than half of those reported in women (4,5). Currently, it is estimated that 75 million people in Europe, the United States, and Japan are affected by OP, leading to up to 8.9 million fragility bone fractures. In Mexico, according to data (2010) from the population and housing census bureau, the overall population was 112 million people, 17% of which corresponded to the adult population older than 50 years. Within this population, 17% of Mexican women and 9% of Mexican men showed OP in their lumbar spines, while 16% of women and 6% of men showed OP in their hips, respectively (5,6). Currently, according to data from the 2020 population and housing census bureau, the Mexican population (126 million people) faces an epidemiological transition with an increased life expectancy (overall, 17.46% of the population are already older than 50 years). It is estimated that 10 million individuals are living with OP, meaning that 1 out of every 3 women and 1 out of every 5 men will end up developing OP (7,8). According to these statistics, male OP is considered a growing reason for concern regarding public health, thus prompting the development of clinical practice guidelines for the management of this disease that now address the management and treatment of OP in male patients as well. However, despite the drafting of these guidelines, male OP is still considered an underdiagnosed and undertreated disease (9). Although the clinical signs between men and women are similar, some characteristics are specific to male OP. For example, in most cases, the type of OP is "secondary," meaning it originates as a direct consequence of other diseases, use of drugs, or lifestyle changes. The densitometry criteria for the diagnosis of OP are not well validated, and studies on the effect of various treatments to prevent fractures in men are lacking. There are no health records on trauma, or on the origin fractures either; additionally, men are less prone to falling. Also, men's life expectancy is shorter, meaning that the therapeutic actions used in men are different from those used in women (10). Therefore, the objective of this study is to conduct a narrative review on the role of sex hormones, their impact on bone mineral density, and their role in the development of male OP.

BONE GROWTH

Bone is a highly specialized type of connective tissue whose main function is to provide mechanical support for muscle activity and physical protection of internal tissues and organs. Also, it plays a key role maintaining homeostasis and serves as a mineral reservoir at systemic level (11). During growth, significant differences can be seen between men and women in the early stages of life. Bone growth is impacted by various factors such as sex hormones, the level of physical activity, and body size. Adolescence is the stage that possibly has the greatest impact on the formation and development of the skeletal system in both men and women. During puberty, boys enter this stage later than girls, and it lasts longer, which could lead to differences in bone growth between the 2 genders. An example of this is that men tend to have longer legs than women because epiphyseal fusion occurs later in men due to a longer period of bone maturation (12). On the other hand, sex hormones also have an impact on growth, bone homeostasis, and the completion of bone maturation. In men, testosterone plays a key role in developing larger skeletons, while estrogen has been associated with less bone resorption, thereby preserving bone mass. However, it has been reported that testosterone also improves bone formation and may be associated with less bone tissue resorption, which could be due to the conversion of testosterone into estrogen, suggesting that while estrogens may be responsible for preserving bone mass, testosterone may be responsible for increasing it. These functions of sex hormones in male development bring about several advantages as they reach adulthood. They help protect bones from fragility fractures compared to women, allowing them to achieve a much higher peak bone mass, larger bone size, and greater bone strength (13).

STROGENS INVOLVED IN BONE GROWTH

Estrogens are a family of steroid hormones including estradiol, estriol, and estetrol. Estradiol (E_2) is the most common and active estrogen there is, and is basically produced by the ovaries. However, adipose tissue, testes, the suprarenal cortex, and the liver also contribute to its production. Estrogens have been associated with maintaining bone mass, and clinical observations have established that estrogen deficiency in bone mass is also a cause of OP in men, suggesting their universal role in bone metabolism (14). The effects of estrogens on bone mass are mainly attributed to their activity inhibiting osteoclast-induced bone resorption. Various in vitro studies using osteoblast cell lines and stromal cells show that estrogens reduce the production of osteoclastogenic cytokines and increase the expression of factors that inhibit osteoclastogenesis (15,16). Still, the effect estrogens may have on bone formation re-

mains unclear, as stromal cells and osteoblasts express estrogen receptor alpha (ERα) and beta (ERβ), which can affect differentiation and bone formation. Osteoblasts are derived from mesenchymal stem cells (MSCs), which can also produce adipocytes, suggesting a regulatory mechanism that determines the lineage between osteoblasts and adipocytes, which could be a critical component in the regulatory pathway of osteoblastogenesis (17). Increased lipid concentration in the bone marrow has been associated with age-related bone loss, which involves the existence of an inverse relationship between adipogenesis and osteoblastogenesis (18). Additionally, it has been reported that ovariectomy-induced osteopenia is associated with an increased adipogenesis. Therefore, in various in vitro studies, it has been hypothesized that estrogens negatively regulate the expression of lipoprotein lipase (LPL), a typical marker of adipocyte differentiation. Therefore, estrogens may be regulating bone formation by inactivating the bone marrow stromal cells of mesenchymal origin to induce lineage switching toward osteoblasts (19). On the other hand, it is believed that the primary goal of estrogens is to inhibit osteoclast-induced bone resorption. Osteoclasts are multinucleated giant cells whose primary function is to degrade the bone mineral matrix during the bone remodeling resorption phase (20). The recruitment of osteoclast precursors, differentiation, and resorption activity are controlled by local factors such as vitamin D, prostaglandins, TGF-β, IL-1, IL-6, and TNF-α, which stimulate osteoclast differentiation and activity through direct or indirect mechanisms. Calcitonin, however, inhibits their activity. The fate of osteoclasts after bone resorption is still unknown. Factors like calcitonin inactivate osteoclasts without inducing cell death, whereas bisphosphonates and vitamin K2 induce osteoclast cell death. The effect estrogens have on osteoclasts is believed to be indirectly regulated through non-osteoclastic cells. Lower estrogen levels during menopause or due to ovariectomy are associated with elevated levels of IL-1, IL-6, and TNF-α and lower levels of TGF-β due to peripheral blood monocytes, bone marrow stromal cells, and osteoblasts (21). Other factors are also involved in osteoclast differentiation and activation, being the receptor activator of nuclear factor kappa B (RANK) one of the key signaling pathways. RANK, which is expressed in osteoclasts, becomes activated when it binds to the receptor activator of nuclear factor kappa B ligand (RANKL). In this mechanism, the osteoprotegerin (OPG) protein also serves as a decoy for RANKL, suppressing osteoclast differentiation activation. Estrogens can regulate RANKL and promote the expression of OPG, thus reducing bone resorption by changing the expression of human osteoblast cellular proteins, including some members of the Wnt/β-catenin signaling pathway, which negatively regulate osteoclastogenesis and mediate anabolic effects on the bone (22,23). Additionally, estrogens inhibit osteoclast differentiation and promote osteoclast apoptosis by increasing the production of TGF-β. In the absence of estrogens, RANKL expression is induced, thus triggering osteoclastogenesis (24) (Fig. 1A).

THE ROLE OF ANDROGENS IN BONE GROWTH

The term "androgen" refers to testosterone and its cholesterol-derived precursors. Testosterone is a predominant androgen in men, secreted in 95% by the testes and 5% by the suprarenal glands through the conversion of dehydroepiandrosterone (25). Testosterone binds to albumin and sex hormone-binding globulin to allow for its local conversion to 5α-dihydrotestosterone (DHT) through peripheral tissues, which have a high affinity due to the abundance of androgen receptors (AR) they have. Testosterone exerts strong anabolic and androgenic effects that impact both men and women, significantly influencing bone growth and maintenance. A study demonstrated that the administration of testosterone in murine models led to a wider epiphyseal growth plate, and these effects were independent of growth hormone and insulin-like growth factor-1 (IGF-1). Similarly, the role of testosterone in bone growth was seen (26). Testosterone has also been shown to play a crucial role in maintaining bone mineral density (BMD) in older men (27). However, serum testosterone levels in older men decrease by 1% per year, which may lead to the clinical symptoms of late-onset hypogonadism (LOH), which is characterized by depression, irritability, sexual dysfunction, decreased lean body mass, and decreased BMD, which may be associated with aging. Therefore, testosterone replacement therapy has been proposed to improve the quality of life of older men with LOH (28). As mentioned earlier, estrogens are necessary for BMD maintenance, and in women, estrogen levels decrease significantly during menopause. In contrast, testosterone levels in men decrease slowly with age, allowing for the stable maintenance of BMD over a longer period of time, which is why OP is more common in postmenopausal women than older men (29). In bone metabolism, testosterone plays a crucial role as it is converted into highly active DHT through 5α-reductase in the cytoplasm of target cells, allowing it to bind to androgen receptors (AR) and inducing androgenic activity. Additionally, testosterone can also be converted into E_2 due to aromatase activity, which allows it to bind to estrogen receptor subtypes (ERα and ERβ), which are associated with bone metabolism. ARs are present in chondrocytes and osteoblasts, with their expression levels varying depending on each individual's age and bone sites. The binding of testosterone to

ARs in osteoblasts promotes bone formation through the indirect activation of cytokines and growth factors. Osteoblasts synthesize various cytokines that promote bone resorption, such as IL-6 and TNF (30). Androgens also positively regulate the TGF-β and IGF growth factors that stimulate bone formation (31). It has been reported that testosterone deficiency promotes the expression of RANKL in osteoblasts, subsequently activating osteoclast differentiation and increasing bone resorption, resulting in reduced BMD. Chondrocyte and osteoblast differentiation and proliferation are induced by the binding of IGF-1 to insulin-like growth factor-binding protein (IGF-BP), which along with chondrocyte apoptosis suppression promotes bone formation. Therefore, testosterone positively regulates the expression of IGF-1 and IGF-BP in osteoblasts (32). Testosterone can also regulate osteoclastogenesis by suppressing the activity of interleukin (IL) 6, which is responsible for osteoclast activation and bone resorption. Therefore, lower levels of testosterone negatively affect BMD. Interestingly, higher levels of AR expression have been reported in osteocytes, the most abundant cells inside the bone, which have been shown to produce various mediators that can influence osteoclastogenesis, such as nitric oxide, TGF-β, prostaglandins, or RANKL. Estrogen and androgen deficiencies lead to a higher prevalence of osteocyte apoptosis (33), which can indirectly stimulate osteoclastogenesis by inducing stromal/osteoblastic cells to secrete RANKL. Additionally, osteocytes secrete OPG, which competes with RANK for its receptor on osteoclasts. Osteocytes, like osteoblasts, regulate the secretion of OPG through the Wnt/β-catenin signaling pathway. Mice lacking β-catenin in osteocytes have been reported to be osteoporotic due to an increased number of osteoclasts, a mechanism similar to that reported in humans. Osteocytes control the bone remodeling process by directly and indirectly regulating osteoclast and osteoblast differentiation and function. Any disruption in this process leads to osteoporosis. In this regard, estrogen receptor subtypes ERα and ERβ play a key role in maintaining BMD in men, as estrogens have a greater effect than androgens inhibiting bone resorption. The loss of ERα function and aromatase deficiency in men induce the development of a phenotype with an extremely low BMD, thus leading to estrogen replacement therapy as an option to improve the levels of BMD in adult male patients (35). E_2 is often responsible for regulating osteoclast apoptosis and the function by increasing the expression of tumor growth factor β (TGF- β). Also, the expression of IL-1, IL-6, IL-7, IGF-1, nuclear factor κB (NF-κB), RANK, and tumor necrosis factor α (TNFα) increases, thus reducing osteoblast proliferation and activity. These genes are known targets of the anti-resorptive effect estrogens have on the bone (36) (Fig. 1B).

RELATIONSHIP BETWEEN SEX HORMONES AND BONE FRACTURES

Falls and fractures are a common thing in older men while performing activities of daily living. The search for tools to help prevent fragility fractures has become a major global objective. The occurrence of age-related fractures is primarily due to reduced physical function, including loss of lean body mass, muscle weakness, bone fragility, sarcopenia, and decreased BMD. Recent studies have identified the relationship that exists between testosterone and the risk of fractures. Also, it has been reported that older male patients with osteoporotic fractures have very low testosterone levels compared to control groups of the same age and ethnicity (37,38). Some studies support the hypothesis that testosterone deficiency is associated with an increased incidence of falls, while others reject this hypothesis (39). The most predominant bone fractures associated with a reduced BMD following low testosterone levels can also be due to the relationship among testosterone, muscle strength, and physical performance in men, which could lead to the development of sarcopenia and a higher risk of falling. Currently, it has been established that the relationship between testosterone deficiency and low BMD is much stronger in young adult men with moderate-to-severe hypogonadism (40). However, few studies have been published on the epidemiology of male OP, which may be due to the small sample sizes and potential biases of these studies. Case-control trials comparing the prevalence of hypogonadism between subjects with OP and control groups have shown that OP-induced fractures are more common in patients with hypogonadism compared to patients without this condition (41). Other studies have documented a significant increase in the risk of fragility fractures among patients with low levels of testosterone and E_2. These low levels of sex hormones are associated with muscle atrophy and a reduced total lean body mass. Therefore, it is logical to assume that a loss of muscle function can impair the protective mechanism against falls, thus leading to an increased incidence of fractures in male patients. Currently, it has become widely accepted that bone metabolism disorders in patients with low estradiol levels can increase the risk of fractures, which could be due to a deficit in the transformation of testosterone to estradiol due to aromatase enzyme dysfunction. Some studies have even reported the development of severe male OP due to mutations in the estrogen receptor of the aromatase enzyme (42).

SIGNALING PATHWAYS IN SEX HORMONE-ACTIVATED BONE METABOLISM

E_2 and other steroid hormones are capable of inducing the activation of different signaling pathways by

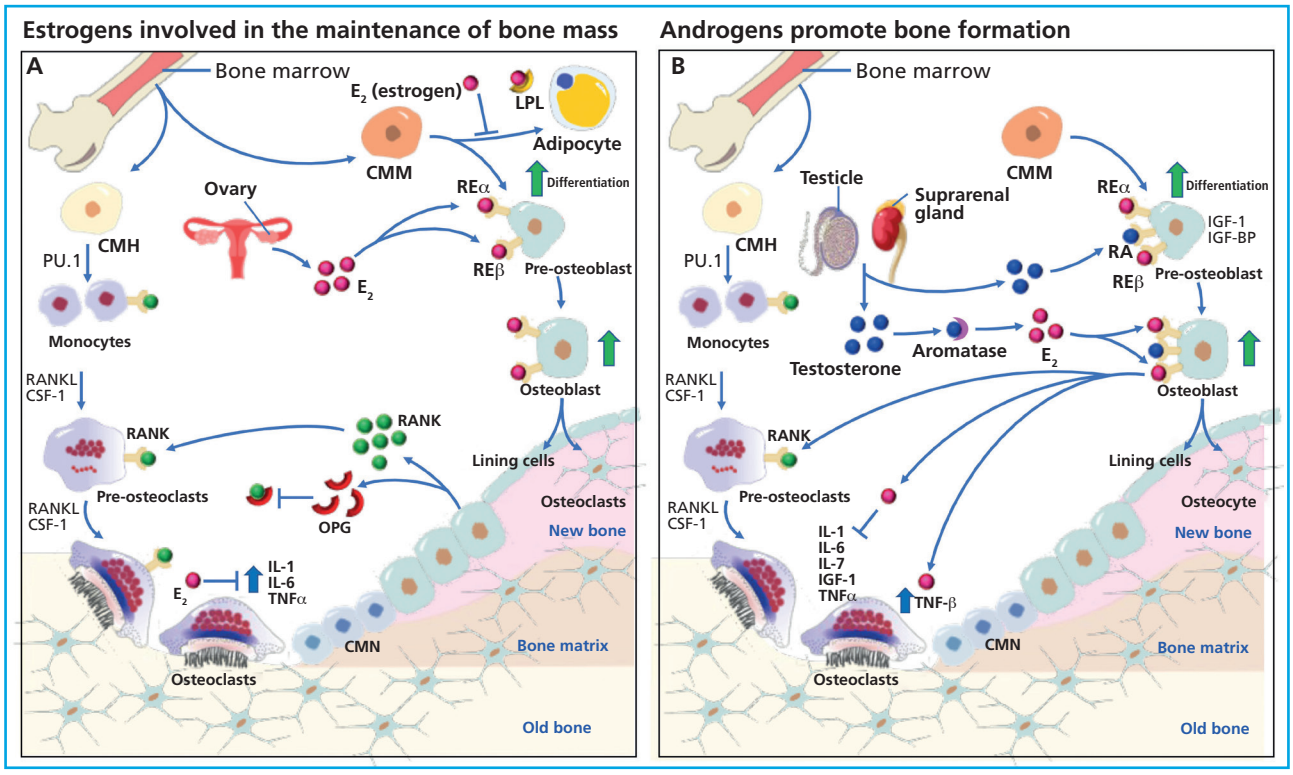

Figure 1. Schematic representation of basic multicellular units (BMUs), their association with bone remodeling, and the role of sex hormones in bone tissue maintenance and growth. The activation of bone remodeling starts with the differentiation of hematopoietic stem cells into mature osteoclasts capable of resorbing bone tissue, where cytokines CSF-1 and RANKL are required at all stages of differentiation. Once bone resorption is completed, there is an attraction of mononuclear cells towards bone remodeling units to recruit osteoblast precursors that will later differentiate into mature osteoblasts and osteocytes, which will become trapped inside the mineralized matrix and function as chemotaxis and mechanosensors. Osteoblasts are bone-forming cells from mesenchymal stem cells and require the activity of various factors for their differentiation, such as sclerostin, the transcription factor RUNX2, and the activation of IGF-1 and IGF-BP proteins. A. It shows the production of estrogens by the ovaries, capable of inhibiting the activity of cytokines IL-1, IL-6, and TNF-α, which are necessary during osteoclastogenesis. In addition, estrogens can bind to the ERα and ERβ present in osteoblast precursors to promote their differentiation and in mature osteoblasts to secrete osteoclastogenesis-inhibiting cytokines such as osteoprotegerin (OPG), which functions as a decoy receptor for RANKL, preventing its binding to osteoclasts and maintaining bone mass. B. It depicts the activity of the testosterone secreted by the testes and the suprarenal gland, which binds to androgen receptors present in osteoblasts and promotes differentiation into mature osteoblasts. Testosterone also acts as an inhibitor of IL-6, which is necessary for osteoclastogenesis, and is turned into estrogens through aromatase, thus promoting osteoblastic differentiation. Additionally, testosterone regulates the expression of cytokines necessary for osteoclastogenesis, thus contributing to the formation of bone tissue.

binding to their receptor through 3 mechanisms: a) classical signaling, where E_2 binds to ERα and ERβ in the cytoplasmic compartment, and then this complex moves to the nucleus where it forms homo- or heterodimers that directly bind to a specific DNA sequence called estrogen response elements (EREs); b) ERE-independent signaling, where the E_2/ER complex moves to the nucleus and interacts with transcription factors to sequester them and change their interaction with DNA, leading to changes in gene expression; and c) non-genotropic signaling (not involving changes to gene expression), in which E_2 sends signals through a G protein-coupled receptor (GPCR) on the plasma membrane. ERs are highly expressed in bone, and their effects have been attributed to receptor-mediated activity. These effects were demonstrated in a study where a group of ovariectomized female mice (OVX) with ERα-/- and a group of orchidectomized male mice (ORX) with ERα-/- did not respond to exogenous estrogen treatment. ERα-/- mice showed about a 10-fold increase in E_2 levels and 5 times higher levels of testosterone, as well as impaired IGF-1 levels, leading to an increased osteoclast activity and, therefore, the development of an osteoporotic phenotype (43). Both the nucleus and the cell membrane have ERα receptors, which activate transcription-independent signaling pathways that are activated by non-genomic mechanisms of ERα, where estrogen exerts antioxidant effects independently. The biological effect of osteo-

genesis is associated with highly specific cellular signaling pathways, including the phosphatidylinositol-3-kinase (PI3K) signaling pathway and protein kinase B (Akt), both of which play critical roles in osteoblasts and bone formation by regulating fundamental cellular processes. The interaction between E_2 and ERα activates the PI3K-Akt signaling pathway, where the PI3K protein is a heterodimeric enzyme made up of a catalytic subunit (P110) and a regulatory subunit (p85), which are necessary for a wide range of cellular activities, including metabolism and aging. On the other hand, Akt is a phosphoinositide-dependent serine/threonine protein kinase. The subsequent interaction of PI3K and Akt are crucial regulators of bone resorption and bone formation by osteoclasts, promoting their differentiation and survival for the maintenance and turnover of bone mass. The deficiency of Akt in osteoblasts induces an apoptosis-susceptible phenotype and suppresses cellular function and differentiation, which is why the PI3K-Akt signaling pathway plays a key role in the bone formation process on the cell membrane (44). On the other hand, the E_2/RE interaction promotes the activation of the mitogen-activated protein kinase (MAPK) signaling pathway, which consists of a set of serine/threonine kinases that regulate a wide range of stimuli. ERK has 2 different isoforms, ERK1 (MAPK3) and ERK2 (MAPK1), both of which are expressed in osteoblasts. ERK is activated by MAP2Ks-MEK1 (MAP2K1) and MEK2 (MAP2K2). Mice with germline deletion of Erk1 and conditional deletion of Erk2 in limb mesenchyme (Erk-1-/-Erk2Prx1 mice), including osteoblasts, exhibit a substantial reduction in bone mineralization, demonstrating the importance of ERK in osteoblast mineralization. Similarly, mice expressing the dominant MEK1 mutation in osteoblasts exhibit low bone mass and hypomineralization of the clavicle and cranial vault. In particular, these mice also display clavicular and cranial hypomineralization, which are reminiscent of mice and humans haploinsufficient for Runx2, the master regulator of osteoblast differentiation (45) (Fig. 2). Another signaling pathway stimulated by the binding of testosterone to the androgen receptor is the renin-angiotensin system (RAS). It has been reported that RAS is a complex system that acts as a mediator between bone formation and resorption through various mechanisms. The role of RAS begins with the conversion of angiotensinogen into angiotensin I (AngI), which is activated by renin, a highly selective protease secreted by the juxtaglomerular cells of the kidney. Afterwards, AngI is converted into angiotensin II (AngII) through the angiotensin-converting enzyme (ACE). The relationship between the renin-angiotensin system and bone metabolism is primarily based on the regulation of AngII in bone. It has been reported that AngII is associated with a significant increase in TRAP-positive osteoclasts and positive regulation of RANKL expression through the extracellular kinase of osteoblasts (46) (Fig. 3). However, these effects are repressed with treatment targeted at ACE inhibition or angiotensin type 1 receptor blockers (ARBs), making the RAS signaling pathway emerge as a strategy in the treatment of bone metabolism disorders such as osteoporosis (47). Currently, the management of OP in men is no different from that indicated in women, and few studies have been conducted on the efficacy of drugs in men. The non-pharmacological treatment of OP is essentially based on lifestyle and does not change between men and women (48). However, the Endocrine Society has formulated specific clinical practice guidelines on the management of male OP, such as bisphosphonates, which are targeted at patients with recent hip fractures, and teriparatide for patients with GI problems and a high risk of fracture. On the other hand, the North American Menopause Society (NAMS) has suggested changes in dietary habits, lifestyle, and initiating pharmacological treatment with bisphosphonates for the management of postmenopausal women—as first-line options—and raloxifene in younger postmenopausal women, to prevent bone loss and reduce the risk of vertebral fractures (49,50).

On the other hand, the effect of androgens on surrogate markers such as TBS or micro-CT has been poorly studied. In a study conducted by Cauley et al. in 2021, the BMD of 211 older men who received moderately low testosterone treatment, without any other reason than age, was analyzed. It was reported that testosterone treatment for 1 year, compared to a control group, significantly increased volumetric trabecular BMD levels. The results were analyzed through quantitative computed tomography (QCT) of the hip and spine, showing an increased estimated bone strength. However, the authors mention that QCT scans are expensive, involve high levels of radiation, and are unlikely to be added to routine clinical practice. Therefore, they propose the use of trabecular bone score (TBS) as an indirect measure of vertebral spine bone microarchitecture, which can be obtained from texture analysis of routine lumbar spine DXA scans and, along with the FRAX® prediction tool, can enhance fracture prediction accuracy and improve an individualized clinical management of OP (51). On the other hand, a study conducted by Movérare et al. in 2003 sought to compare the effect of ER activation on bone in vivo with the effect of AR activation in 9-month-old orchiectomized wild-type mice with ER inactivated by the androgen 5α-dihydrotestosterone. QCT analysis of BMD demonstrated that the bone preservation effect of ER activation and AR activation was of the same degree. However, a more detailed analysis of trabecular bone microarchitecture, using high-resolution micro-CT, showed that ER activation, as opposed to AR activation, preserved trabecular thickness, while AR activation only preserved the number of trabeculae (52). Therefore, these tools can be used to create computer simulations of bone remodeling and dynamically assess a response to testosterone therapy in routine clinical practice.

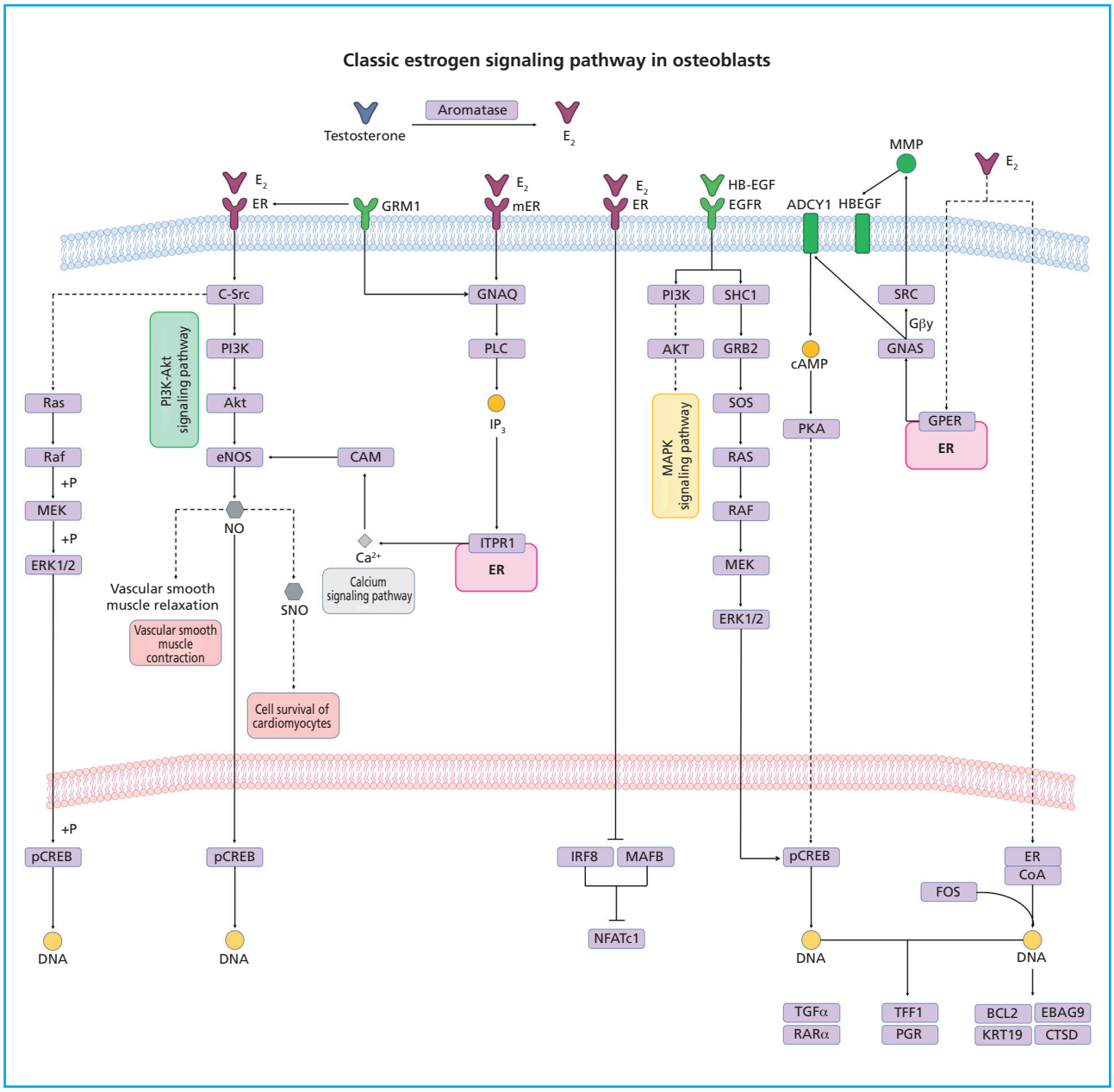

Figure 2. Estrogen receptor signaling. Estrogens diffuse through the plasma membrane binding to ERα or ERβ with nuclear dimerization and translocation. ERs bind to specific sequences, recruit coactivators, and transcribe their target genes. Estrogen-bound ERs can also interact with transcription factors such as AP1, SP1, and NF-kB, which also play a significant role in regulating osteoclastogenesis. The activation of tyrosine kinase receptors (EGFR) and G protein-coupled receptors (GPCRs) leads to the activation of MAPK, PKA, and PI3K-Akt signaling pathways.

CONCLUSIONS

The bone is a tissue that undergoes constant renewal through the process of bone resorption and formation. However, disruptions in this process can lead to the development of diseases like OP. While many studies have recognized the role of estrogen and its interaction with specific receptors as regulators of bone metabolism, androgens have been less examined. Evidence suggests that androgens like testosterone play a key role in maintaining BMD and bone health in men. Additionally, it has been identified that many molecular mechanisms of testosterone operate on the signaling pathways involved in bone metabolism, including the PI3K-Akt, MAPK, and RAS pathways, which have been previously described for the role they play maintaining bone mass. Therefore, the role of testosterone could be explored as a treatment option to improve BMD in older men.

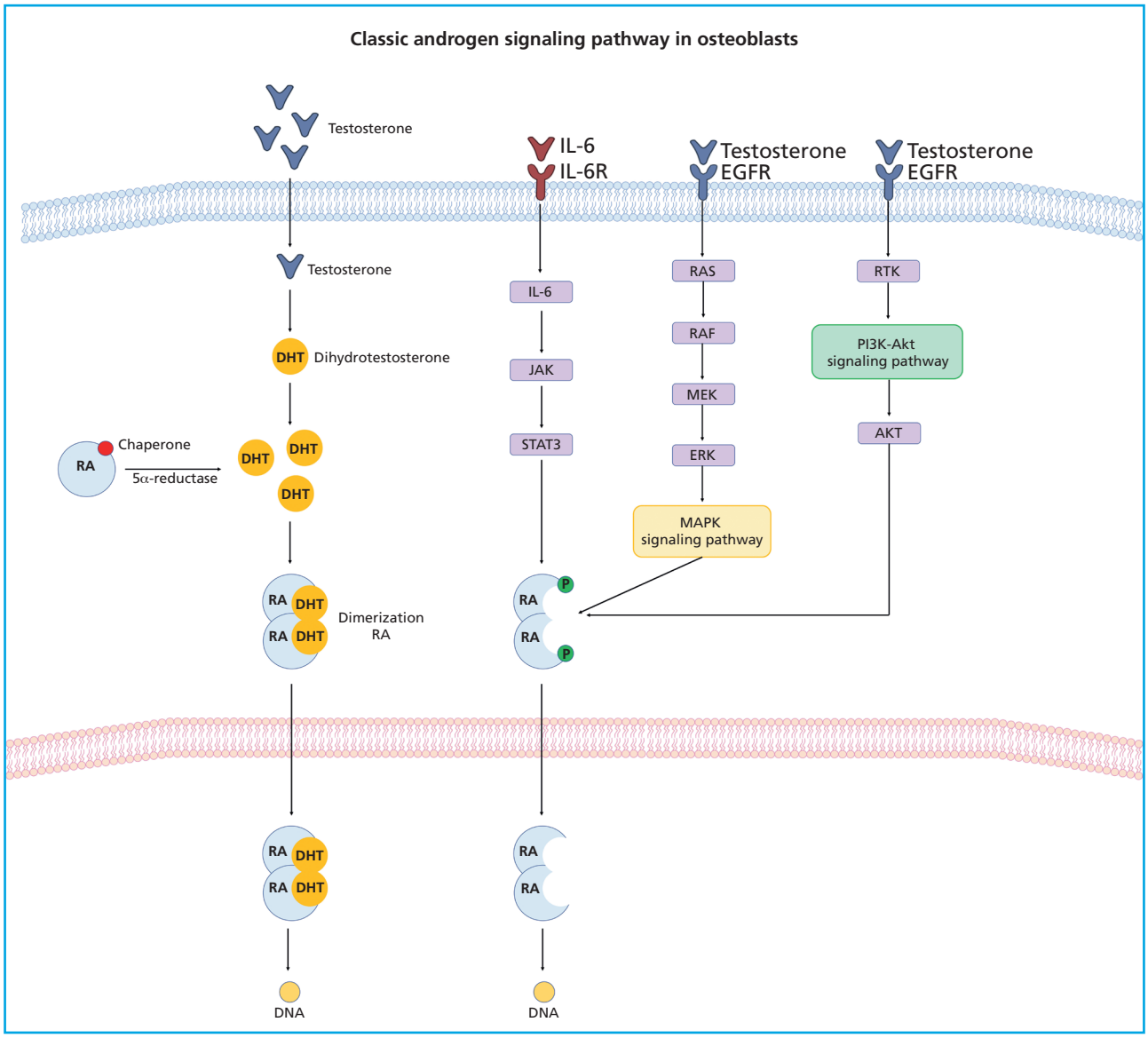

Figure 3. Androgen receptor signaling. The androgen receptor (AR) is kept inactive in the cytoplasm by chaperone proteins. The binding of androgens to the AR lead to the dissociation of the chaperone complex, causing a conformational change in the AR followed by its dimerization. The AR dimer translocates to the nucleus and binds to promoters/enhancers of target genes, thus facilitating transcription through interactions with coregulators. ARs can also affect cell signaling without directly binding to gene promoters. In the absence of androgens, various growth factors and cytokines can also activate the AR by regulating multiple signaling pathways, including the PI3K-Akt and MAPK/ERK-mediated RAS pathways involved in bone formation.

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Special Article

Polygenic risk scores (PRS) – A tool for disease prediction and personalized medicine

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Abstract

Over the past decade, genomics and high-throughput sequencing have revolutionized our understanding of complex diseases. Polygenic risk scores (PRS) have emerged as a promising tool for predicting diseases and personalizing treatments. However, their implementation requires confirmation of real utility, which raises significant ethical and privacy challenges.

PRS are used to identify high-risk individuals and guide personalized treatments. Their potential is evident in diseases such as cancer or osteoporosis, where they improve risk stratification and enable the selection of more effective treatments. However, PRS have multiple limitations, including lack of individual accuracy, variability among different populations, and the inability to account for the impact of environmental factors. Clinical interpretation and ethical, legal, and social implications (ELSI) are highly relevant issues in this field.

In the future, PRS are expected to improve their predictive accuracy by combining clinical risk factors and adapting to populations of various ethnicities. Consequently, PRS are expected to play a central role in personalized medicine.

Keywords:
Polygenic risk scores.
Personalized medicine.
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INTRODUCTION

In the past decade, the advances made in genomics and high-throughput sequencing technology have transformed our understanding of the genetic basis of complex diseases. Polygenic risk scores (PRS) have emerged as an innovative tool that promises to revolutionize disease risk prediction and personalized medicine. These scores are based on the fundamental premise that many complex diseases, including heart disease (1), diabetes (2), cancer (3), or bone tissue disorders (4), result from the interaction of multiple genetic variants, each with a small effect individually. In this context, PRS allow for the calculation of individual genetic risk by adding information from hundreds, or even thousands, of genetic variants scattered throughout the genome (5).

The application of PRS in medical research and clinical care has prompted increasing interest due to its potential to identify individuals at higher risk of developing diseases, which, in turn, can guide early prevention and personalized management strategies. However, the implementation of PRS in the routine clinical practice has significant ethical, legal, and social implications (ELSI) and raises issues of privacy, result interpretation challenges, and the need to consider the clinical context and other risk factors (6).

This review aims to provide a non-exhaustive overview of PRS, from their theoretical foundation to their clinical application, and examine future perspectives and challenges faced in this field. Understanding this revolutionary tool is crucial in the context of disease genomics and has the potential to transform medical practice, providing new opportunities for the diagnosis, prevention, and individualized treatment of complex diseases.

GENERATION OF POLYGENIC RISK SCORES (PRS)

A polygenic risk score (PRS) represents an estimate of an individual's genetic burden related to a specific trait or disease. Its calculation is based on the sum of a subject's risk alleles, which are adjusted based on the effect size of these alleles, as derived from the results of genome-wide association studies (GWAS). The generation of PRS involves a series of fundamental methodological steps. An article published in Nature Protocols back in 2020 provides a detailed description of these steps, serving as a starting point and reference guide for researchers interested in conducting polygenic scoring analyses (7).

First, relevant genetic variants are selected from the GWAS results that have demonstrated a significant association with the disease of interest. Afterwards, these variants are then weighted according to their association strength, assigning weights that reflect their contribution to genetic risk. Subsequently, the "clumping" process groups the multiple variants, while considering linkage disequilibrium (LD) among them so that the SNPs retained are largely independent of each other. Additionally, the "thresholding" process involves applying a threshold to decide which variants are included in the PRS. This is done by considering the association strength of each variant, and if its P value or association statistic exceeds the specified threshold, it is included in the PRS. The PRS is calculated by adding the products of weighted variants by their alleles in the individual's genome. Eventually, its predictive capability is assessed using data from other independent groups (7,8).

In recent years, other methods have emerged to calculate PRS, such as the LASSO (Least Absolute Shrinkage and Selection Operator) method (9), which uses penalized regression to select informative SNPs by adding LD information, and Bayesian regression methods. Both have shown that they can achieve better performance than the "clumping + threshold" (C+T) method (10).

However, there is noticeable variability in the procedures for generating and validating PRS, making it challenging to compare and translate them into clinical care. The ClinGen Complex Diseases Working Group, in collaboration with the Polygenic Score Catalog (PGS), has updated the "genetic risk prediction information reporting" (GRIPS) to show the current state of the field. This document defines the minimum information required to interpret and evaluate PRS, especially in relation to subsequent clinical applications. Additionally, it emphasizes the importance of guaranteeing the availability and transparency of data, thus encouraging researchers to deposit and share PRS through PGS to facilitate replication in other studies (11).

CLINICAL APPLICATIONS

PRS have proven to be versatile tools in a wide range of clinical contexts and applications (Fig. 1). One of PRS prominent applications is the identification of high-risk individuals (11). By calculating a patient's PRS, individuals with significantly higher genetic risk of developing a disease compared to the overall population can be identified. This allows for more precise risk stratification and the possibility of early interventions, such as lifestyle changes, screening tests, or pharmacological prevention measures capable of reducing the incidence and severity of the disease.

Conventional non-genetic risk models typically add clinical and laboratory factors to identify high-risk individuals who are eligible for selective prevention

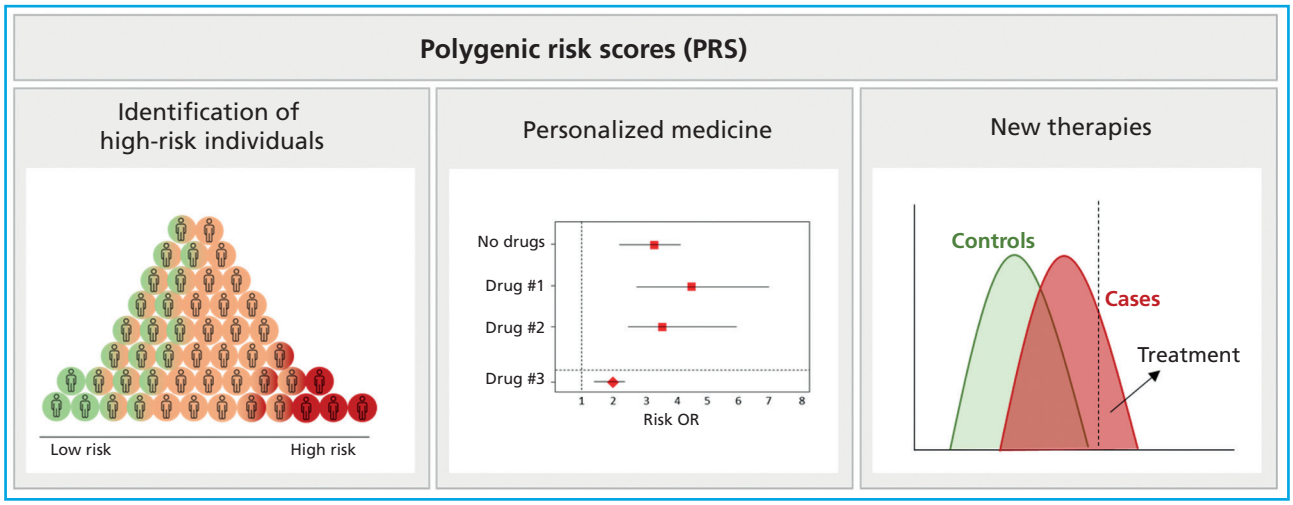

Figure 1. Illustration with the summary of the clinical applications described in this manuscript.

strategies or prescription of medications to reduce the risk of disease. However, these factors fail to detect a significant number of individuals who will eventually develop the disease. For example, with cardiovascular risk calculators, almost 40 % of all individuals who will eventually suffer from heart diseases go unnoticed, especially if they are young individuals (12). Regarding breast cancer, the multiple factors used provide relatively weak predictions, identifying only a small proportion of individuals with long-term high risk (13).

In the field of metabolic bone diseases, the Fracture Risk Assessment Tool (FRAX) is a widely used tool to assess fracture risk. After initial analysis and validation in Spanish women without bone mineral density (BMD) analysis, the FRAX had a poor discrimination ability to predict major fractures but a good discrimination ability to predict hip fractures based on the area under the ROC curve. Nonetheless, the FRAX predictive ability is not much better than that from simple models based on age and BMD (14). More recently, using U.S. cut-off values, researchers confirmed that the FRAX performed better identifying patients who would not sustain major osteoporotic or hip fractures within the next 10 years compared to those who would. A considerable number of patients who developed major fractures were not identified in the initial assessment of the FRAX (15). In other words, based on these results, the FRAX specificity would be higher compared to its sensitivity.

Some studies have evaluated PRS along with the FRAX, as is the case with the PRS known as gSOS, which is related to fracture risk (16). The authors demonstrated that gSOS predicted the occurrence of a major osteoporotic, or hip fracture better than most traditional clinical risk factors, including previous fractures, use of corticosteroids, rheumatoid arthritis, and smoking, although always below the prediction level of BMD. They also demonstrated that adding gSOS to the FRAX improved the FRAX risk prediction ability, although still falling below the prediction level of FRAX + BMD (16). In a recent study, we analyzed the ability of 4 different PRS to predict osteoporosis among the Spanish population. We found that the osteoporosis group had a significantly higher genetic risk compared to the control group in 3 of these evaluated PRS. This suggests their potential utility in risk-based identification strategies based on a combination of clinical and genetic criteria (17).

Another important application is personalized medicine. PRS can guide the medical decision-making process adapted to a certain individual's genetic characteristics. PRS can help determine the optimal approach to treatment, selecting specific therapies that fit the patient's genetic profile and predicting what the patient's therapeutic response will be. In a study of therapies vs advanced breast cancer, the authors generated a final model with 13 single nucleotide polymorphisms (SNPs), which, when combined with the clinical covariates, showed predictive capability with a time-dependent area under the curve (AUC) of 0.81, compared to an AUC of 0.64 for the model with clinical covariates alone (18). This type of work demonstrates the potential of PRS in the field of pharmacogenomics to guide the selection of drugs and optimal dosages to maximize efficacy and minimize side effects. A systematic review aimed at obtaining information on the performance of PRS in predicting therapeutic outcomes identified a total of 89 articles that added pharmacogenetic variants into polygenic models. The authors could confirm that almost all studies found a significant association between their polygenic model and the outcome of the investigated medication (93 %). However, less than half (47 %) compared the performance of the polygenic model with clinical predictors, and only 40 % validated the model's predictions in an independent cohort (19). Manousaki et al. have explored the application of the previously described PRS-gSOS (16) as an independent risk factor for

the occurrence of fractures in users of anti-osteoporotic drugs. They showed that patients with gSOS below average had increased adjusted odds (54 %) of sustaining major osteoporotic fractures and twice the adjusted odds of sustaining hip fractures compared to those with gSOS above average. Therefore, they demonstrated that PRS-gSOS is independently associated with incidental fractures among patients treated for osteoporosis (20).

All in all, although many association analyses have been conducted between polygenic risk and drug response in various fields such as anticoagulation, neuropsychiatric disorders, cancer, or various metabolic disorders (21), there are still many key considerations that should be made to improve and facilitate translation into the clinical setting of studies like these.

PRS are also used in the research of new therapies. By identifying individuals with a high genetic risk of a certain disease, PRS enable the selection of participants for prevention and treatment clinical trials. This facilitates the investigation of new therapeutic interventions, both pharmacological and non-pharmacological, with a specific focus on high-risk populations, thus accelerating the development of more effective treatments (22). Additionally, PRS contribute to the understanding of the genetic basis of these diseases, providing insights into the underlying biological pathways, which can lead to a better understanding of their pathogenesis and, ultimately, the development of more effective prevention and treatment (21,23).

LIMITATIONS

Despite their potential and utility in disease genetics and personalized medicine, PRS have several limitations that must be considered in their application and analysis. One of their main limitations is limited accuracy in individual prediction. Although PRS can provide an estimate of a person's genetic risk for a given disease, this estimation is relative and does not guarantee the occurrence of the disease. Genetic risk is only one of the various factors that impact the onset of complex diseases that does not taken into account environmental, lifestyle, or other risk factors that also play a crucial role. Therefore, they cannot be used exclusively to predict disease occurrence (24). The data analysis tools available today and the size of the cohorts available do not yet allow for in-depth analyses to consider the possible interactions between multiple genetic and environmental factors.

Additionally, the accuracy of PRS can vary depending on the population and ethnicity at stake. Most genome-wide association studies (GWAS) have been conducted in populations of European ancestry, which may limit the applicability of PRS in more diverse populations. In fact, several studies suggest that differences in the genetic structure of various populations can have an impact on the accuracy of PRS and may require specific adaptations for each population group (25,26).

Another important limitation is related to clinical interpretation. The information provided by PRS can be difficult to interpret for physicians and patients alike. PRS-based clinical decision-making requires a solid understanding of genetics and epidemiology, which may not be available in all clinical settings. Additionally, communicating PRS results to patients raises ethical and genetic counseling challenges (6,11).

ETHICAL AND PRIVACY CONSIDERATIONS

PRS raise important ethical and privacy issues. The personal genetic information contained in a PRS is sensitive and must be handled with caution. Protecting an individual's privacy and the safety of genetic data are critical issues when implementing PRS in the health care setting (27).

On the other hand, the implementation of PRS emphasizes the importance of properly communicating results to patients. Information on a person's genetic risk can be useful but can also generate anxiety and stress, especially if the interpretation of these results is not clear or if they are not accompanied by effective management recommendations. Appropriate genetic counseling and the communication of results in a judicious, understandable, and sensitive manner are essential to ensure that patients understand the meaning of their PRS and can make informed decisions on their health (11).

The privacy of genetic data is a critical concern in the use of PRS. Genetic information is highly sensitive and can reveal personal data such as ancestry and individual genetic characteristics. Protecting the privacy of genetic data is essential to prevent the misuse of this information, including genetic discrimination in areas such as employment or health insurance (28). Data safety is another concern. Genetic information must be stored securely to prevent unauthorized exposure or data theft. Implementing robust security practices and data encryption is essential to protect the privacy of all individuals and prevent vulnerabilities in the management of genetic data (29).

Finally, equity in access to genetic information is another relevant ethical issue. The availability of PRS can be biased toward those who have access to genetic sequencing services, thus leaving certain population groups behind. Ensuring equitable and fair access to PRS is a significant ethical challenge (30).

FUTURE PERSPECTIVES

The field of PRS continues to evolve and promises to play an increasingly relevant role in clinical genetics and precision medicine. Future perspectives in the field of PRS focus on improving the risks and limitations mentioned earlier. Greater predictive accuracy is required, which will improve as more evidence accumulates and more sophisticated models are developed. Adding whole-genome sequencing data and identifying rarer and lower-effect variants could significantly increase the predictive ability of PRS. Adaptation to diverse populations through the inclusion of data from different ethnic groups and populations will allow for a broader application of PRS on a global scale and improve their accuracy in non-European populations.

In the short term, and as can already be seen in various reports on different fields of medicine, including skeletal diseases, there are promising PRS, and it is likely that new PRS with greater sensitivity and specificity will emerge. These PRS, along with other risk factors (clinical, analytical, or imaging), could improve the stratification of patients at risk of bone fractures and design personalized preventive strategies. Something similar has already been implemented in some cancers, where strategies that combine gene panels and clinical factors are used to determine individual risk (31,32).

As PRS become more widespread, there will be more intense ethical and legal discussions on issues such as privacy, genetic discrimination, and equity in access. It will be essential to address these issues effectively and promote policies that protect individuals' rights.

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Case report

Calcinosis *cutis*

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Abstract

Case report: we report the case of a 48-year-old woman with pain in the maxillary sinuses and temporal areas. The presence of subcutaneous facial calcific plaques was confirmed in computed tomography (CT). Both the physical examination and the lab test results were within normal limits. Upon further questioning, the patient mentioned that she had been administered a facial filler product containing calcium hydroxyapatite (CaHA) (Radiesse®) the year before.

Discussion: CaHA microspheres are radiopaque, making them visible through conventional x-rays, especially CT scans. The characteristic imaging features, typically bilateral and separate from the bone, along with the history of previous injection of this material, should help the clinician recognize this finding and isolate it from other conditions and diseases. Because of the popularity of this facial rejuvenation technique, clinicians should be familiar with the imaging characteristics associated with the deposition of this substance.

Keywords:
Calcinosis.
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INTRODUCTION

Calcinosis *cutis* is a rare disorder characterized by insoluble calcium salt deposition in cutaneous and subcutaneous tissues. This disorder can be due to multiple processes, including connective tissue diseases, tumors, and trauma. Patients may present with visible skin abnormalities such as papules, nodules, or plaques, which can sometimes ulcerate, releasing some sort of whitish material, or may be incidentally diagnosed through imaging modalities or histological findings (1). We hereby report the case of a woman with subcutaneous facial calcifications associated with the administration of a biodegradable and resorbable filler containing calcium hydroxyapatite microspheres (Radiesse®).

CASE REPORT

We report the case of a 48-year-old woman referred to our hospital with oppressive pain in both maxillary sinuses and temporal areas over the past few months, radiating across her entire face. She was initially evaluated by the Otorhinolaryngology unit that ordered a facial and paranasal sinus computed tomography (CT). The CT scan revealed the presence of calcific plaques of facial subcutaneous fat location spreading from the nasal commissures towards the auricular region on both sides (Figs. 1 A and B), which triggered her referral to our center.

The patient's past medical history included smoking in her youth, but no other known toxic habits or allergies. She had a history of hypercholesterolemia, migraines, and adjustment disorder, left intercostal neuropathy, and left eye amblyopia. Six years prior, she had been diagnosed with a tubular carcinoma in her left breast, which was successfully treated with surgery (tumorectomy), radiation therapy, and hormone therapy. She was currently on drugs, including desloratadine, almotriptan, diazepam, desvenlafaxine, mirtazapine, paracetamol, and amitriptyline. The physical examination was normal. Complete blood count, erythrocyte sedimentation rate (ESR), routine biochemistry including calcium, phosphate, magnesium levels, proteinogram, and urine element and sediment analysis all fell within normal limits. Ionized calcium, 25-hydroxy-vitamin D (25(OH)D), parathyroid hormone (PTH), procollagen type 1 N-terminal propeptide (P1NP), C-terminal telopeptide of type 1 collagen (CTX), and angiotensin-converting enzyme (ACE) levels also fell within normal ranges. Upon further inquiry, the patient mentioned that she had been treated with a dermal filler product (Radiesse®) for wrinkle correction in the malar, labial commissure, and chin areas one year prior. Also, that this procedure was repeated 3 months later, being the product also administered in both temporal regions. Three years later, a new follow-up imaging study confirmed the clear reduction of calcium deposits in the facial area (Figs. 1 C and D).

DISCUSSION

Radiesse® (Merz Pharma GmbH & Co. KGaA, Frankfurt, Germany) is a biodegradable resorbable filler that contains calcium hydroxyapatite (CaHA) microspheres suspended in a carrier gel to stimulate the endogenous production of collagen (2). Experimental research on animals has demonstrated that this neocollagenesis appears on week 4 and goes on for, at least, 12 months after the injection (3). In fact, in individuals receiving these fillers, the effects of CaHA injections remain visible for nearly 18 months.

Since it was approved by the Food and Drug Administration (FDA) back in 2006, CaHA has been used in plastic and reconstructive surgery to augment the deep dermal and subdermal soft tissue of the facial area, smoothing out wrinkles. It is also used to restore or correct the signs of facial fat loss (lipoatrophy) in individuals infected with the human immunodeficiency virus (HIV), and for soft tissue augmentation in other cutaneous areas (neck, arms, buttocks, etc.) (4). Good results have been documented in the medical literature available after the use of CaHA, and patient satisfaction scores are high. Also, CaHA has a good safety profile, although transient adverse events such as bruising, swelling, redness, pain, and itching at the injection site have been reported. Also, in up to 3% of the cases, nodules can become evident, which in most cases are not visible and resolve without further treatment (5).

The calcium present in CaHA microspheres makes them radiopaque. However, a trial conducted back in 2008 (6) demonstrated that CaHA is not always visible in conventional x-rays, while indeed it is easily recognizable in CT scans immediately after the injection. A similar phenomenon occurs when analyzing magnetic resonance imaging (MRI), where CaHA deposits appear as a low-to-moderate intensity signals (7) that often disappears 2 and a half years later.

Therefore, we should understand the characteristics of CaHA deposit images to differentiate them from other conditions that have a similar radiographic appearance, such as myositis ossificans, dystrophic calcifications, milia-like osteomas of the skin, and foreign bodies (8). However, CaHA deposits should not pose any diagnostic challenges, especially if the radiologist knows the patient's health record. The traditionally bilateral presence of the material, which separates from the bone, along with a history of prior injection of this product, should help the clinician make accurate diagnoses. There is no evidence that CaHA migrates or that osteogenesis is stimulated after placing the filler at deep dermis and subcutaneous level. How-

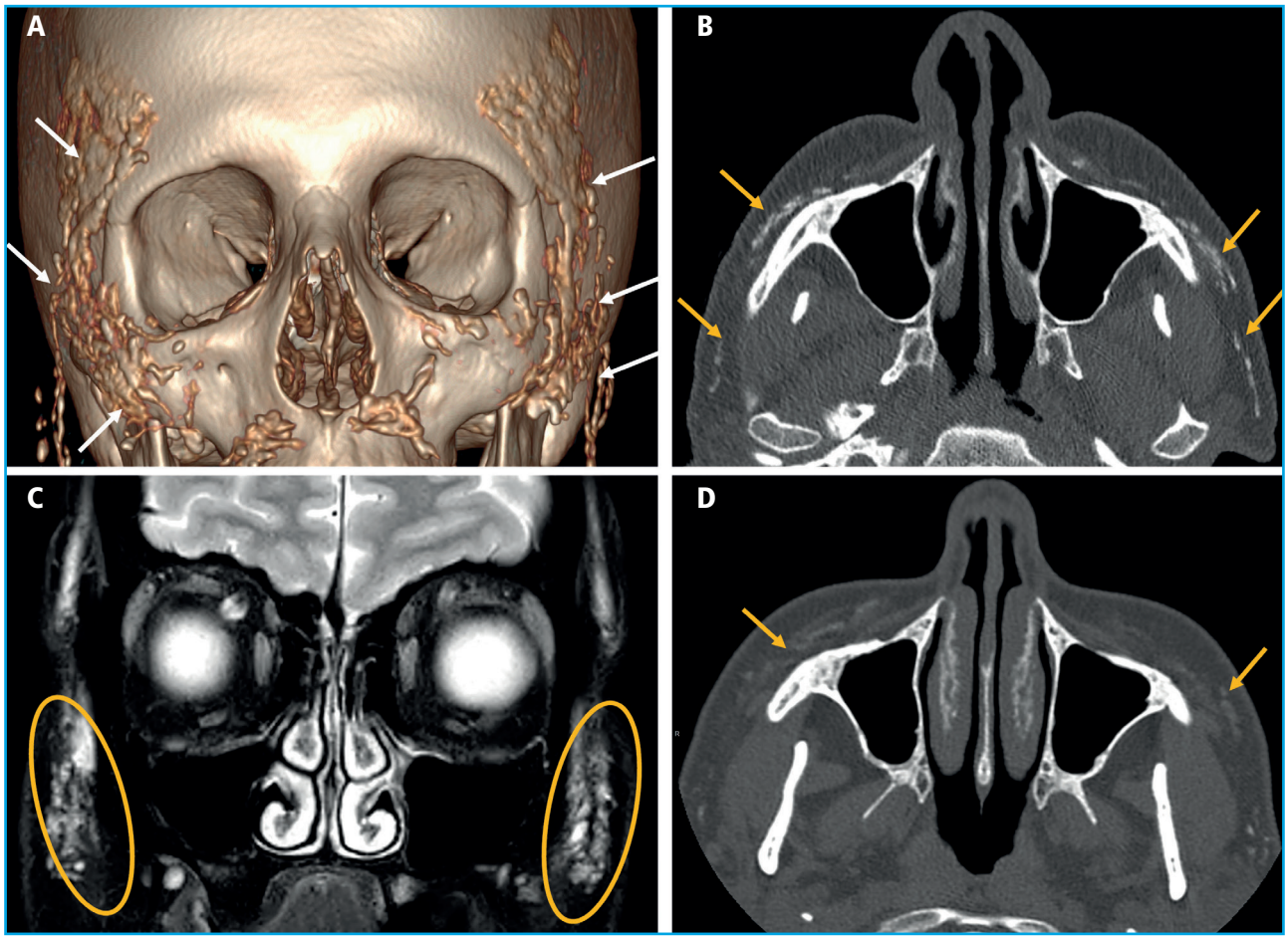

Figure 1. A. 3D reconstruction of a facial CT scan. B. Axial image of a facial CT scan without contrast. C. Coronal image of a T2-weighted fat-saturated magnetic resonance imaging (MRI) sequence. D. Axial image of a facial CT scan without contrast 3 years after the Radiesse® injection. Multiple hyperdense foci are evident in the CT scans (A and B), diffusely distributed across the subcutaneous cellular tissue of, predominantly, the zygomatic, infraorbital, and buccal regions, corresponding to calcium hydroxyapatite deposits. The MRI (C) shows these deposits overtly hyperintense on the T2-weighted imaging. Significant product resorption can be seen after 3 years (D), with thin residual deposits.

ever, we should mention that, over time, the resorption of CaHA microspheres can lead to a reduced radiodensity of the filler material (6).

The popularity of soft tissue fillers for facial rejuvenation has increased significantly over the past few years. In fact, dermal fillers have become one of the most popular clinical esthetic therapies, with 2.6 million injections administered in the United States alone back in 2018 (9). The popularity of soft tissue fillers is partly due to being a quick, less invasive, and technically less complex procedure compared to surgery. In 2018, the most widely used fillers in the United States were hyaluronic acid and CaHA (9). This type of esthetic treatment has also gained popularity in our country (10). Therefore, clinicians should become familiar with the imaging characteristics associated with the deposition of this substance. The case presented here should help clinicians recognize this finding and differentiate it from other conditions and diseases.

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