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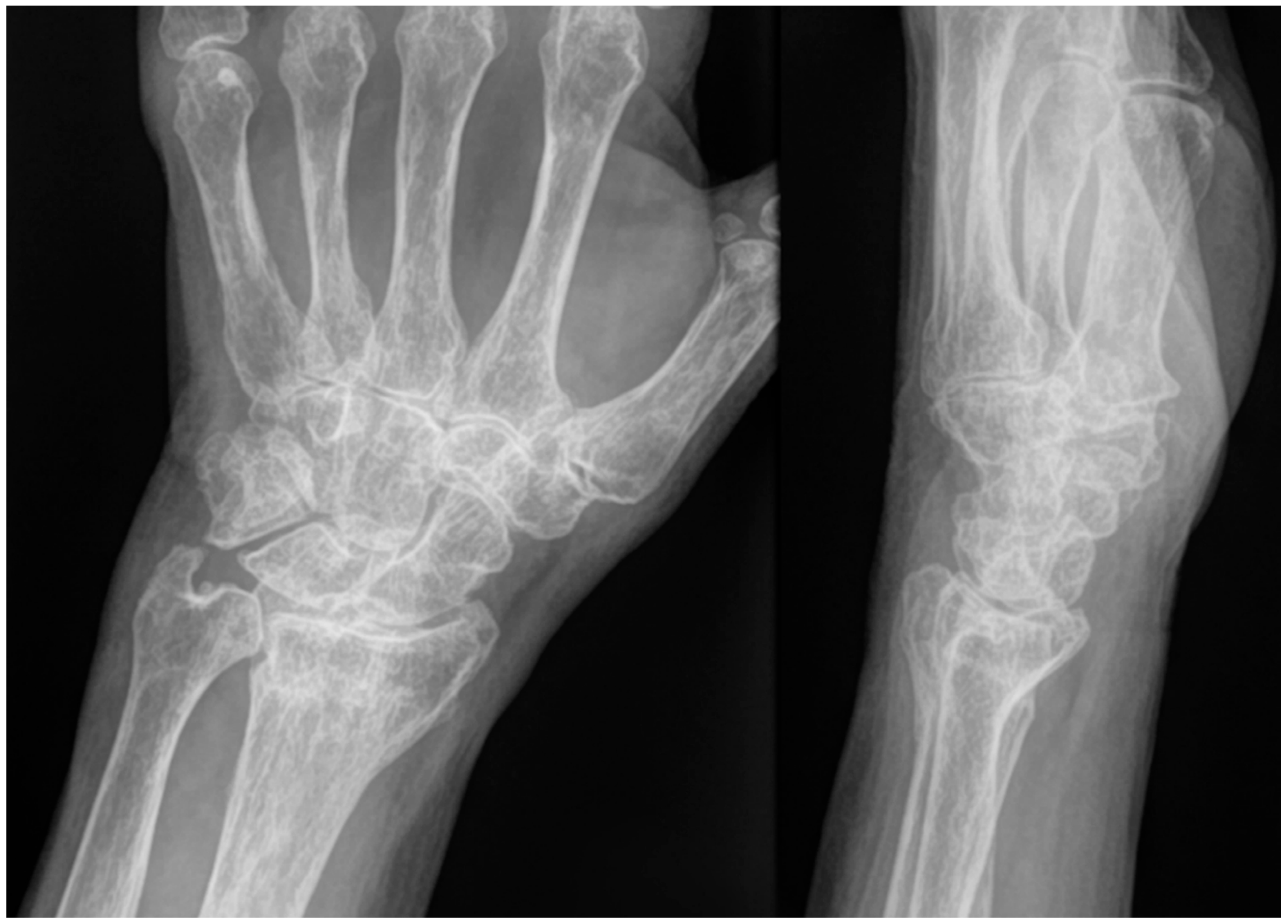

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Summary

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Cover image:

Follow-up radiographic control after three months of treatment: consolidated distal radius fracture.

Andrés Toribio AM, Cid-Bassaletti C, Costa Segovia R. The dark side of wrist fractures. Rev Osteoporos Metab Miner 2026;18(1):37-44. DOI: 10.20960/RevOsteoporosMetabMiner.00096

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Sequential therapy and stratified risk of osteoporotic fracture

Osteoporosis is a chronic disease defined by a reduction in bone strength that predisposes individuals to fractures. The risk of fracture determines the indication for treatment. This risk is not constant but rather changes throughout life depending on associated comorbidities and the nonpharmacological and pharmacological measures that are implemented (1).

The therapeutic armamentarium available for the treatment of osteoporosis is broad, with the primary objective of reducing the number of fractures while maintaining acceptable adverse effects in relation to the benefit obtained. On the other hand, antiosteoporotic drugs have a limited duration of effect, either due to regulatory agency restrictions, decreased efficacy over time, or serious adverse effects, whereas the duration of the disease itself is prolonged. Moreover, most of these drugs, with the exception of bisphosphonates, have transient effects, losing their benefit once treatment is discontinued. This necessitates the use of sequential therapy (2), which consists of the successive use of different drugs in order to maintain their effectiveness. The sequence employed is determined by fracture risk and the individual clinical situation of each patient. Of note, osteoporosis treatment is long-term and may last throughout the patient's lifetime, depending on the persistence of fracture risk (3).

Numerous factors determine fracture risk, but to establish risk groups, different clinical guidelines have used age, prior fracture, and bone mineral density (BMD) (4,5). Age is a key factor, as for similar BMD values, fracture risk increases with age, and the incidence of different fracture types changes: distal radius fractures are more prevalent in younger women, whereas vertebral and hip fractures predominate in older populations (6). Although a high proportion of fractures occur in individuals with BMD values in the osteopenic range, BMD—particularly at the hip—is a determinant of fracture risk. This was recently confirmed by the SABRE study, which included data from more than 50 clinical trials encompassing 50 000 fractures (7). Probably the most influential factor is a prior fracture, which increases the risk of new fractures, especially during the first two years after the initial fracture, although the risk persists throughout the patient's lifetime (3,5). A study conducted in our health area, including 276 postmenopausal women followed for eight years and analyzed using machine learning techniques, showed that prior fracture was the variable with the greatest weight in fracture risk; these data were validated in a general population cohort (8). Based on these findings, SEIOMM established three risk categories: moderate, high, and very high (4). The position of ASBMR-BHOF is similar, taking into account the presence or absence of fractures, the time elapsed since fracture, and fracture location (5).

In patients at moderate risk, initial therapy with a selective estrogen receptor modulator (SERM) is recommended; however, age modifies risk, and treatment should subsequently be continued with a drug that reduces hip fracture risk, such as bisphosphonates or denosumab (1). Patients at high risk modify their initial therapy depending on three situations: intolerance to oral bisphosphonates, duration of previous therapy, and treatment failure (9). In the first situation, continuation with a parenteral antiresorptive agent—zoledronate or denosumab—is recommended, achieving a reduction in bone remodeling and an increase in BMD. Bisphosphonates show greater efficiency during the first five years; beyond this period, they maintain bone mass but do not increase it, although their antifracture efficacy likely persists for up to ten years (10). Parenteral zoledronate maintains this benefit when used for six years, whereas denosumab produces a continuous increase in bone mass; however, after ten years, data on fractures and safety are lacking (2). Of note, the baseline hip T-score when selecting therapy, as the likelihood of achieving a T-score > -2.5 varies depending on the drug used. In this group, the presence of treatment failure shifts the patient into the very high-risk category and should be managed accordingly.

A special situation in sequential therapy arises after denosumab discontinuation, to avoid the development of multiple fractures. A bisphosphonate should be used—oral for treatment durations shorter than two and a half years (11) or intravenous zoledronate for longer periods (12). Real-world studies have shown the benefit of zoledronate in preventing multiple fractures. An anabolic agent should not be used in this context, as it would increase bone remodeling and thereby raise the risk of multiple fractures.

Patients at very high risk require initial sequential therapy with an anabolic or dual agent (teriparatide, abaloparatide, or romosozumab), followed by an antiresorptive drug. In treatment-*naïve* patients, a clear benefit is observed compared with monotherapy, whereas in patients previously treated with antiresorptives, the densitometric response is partially blunted, although antifracture efficacy is not diminished (13,14). Among the available anabolic agents, only romosozumab can be used in a subsequent cycle; this is not possible with teriparatide or abaloparatide. With any type of sequential therapy, regardless of patient risk, the final drug in the treatment sequence is a bisphosphonate (10).

In conclusion, sequential therapy is effective in reducing osteoporotic fractures, and the therapeutic regimen should be individualized according to fracture risk, comorbidities, and the patient's clinical situation.

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Original

Relationship between smoking status and the prevalence and progression of abdominal aortic calcification in men

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Abstract

Introduction and objective: abdominal aortic calcification (AAC) often precedes the development of coronary artery calcification, contributes to arterial stiffness, and predicts cardiovascular events and mortality. The aim of this study was to evaluate the association between smoking status and the presence and progression of AAC in a male population.

Materials and methods: a total of 306 men aged > 50 years who underwent dorsolumbar radiographic imaging, repeated 4 years later, were selected to determine the presence and progression of AAC. Data collected included age, body mass index (BMI), diabetes status, and smoking history (age at initiation, cigarettes per day, and duration of smoking).

Results: current smokers and former smokers showed a higher prevalence of AAC (52.7 % and 52.6 %, respectively) compared with never smokers (25 %), with former smokers being older. After adjustment for age and BMI, current smoking was associated with AAC prevalence (odds ratio [OR] = 3.95; 95 % confidence interval [95 % CI], 2.00-7.82). A similar association was observed in former smokers (OR, 2.93; 95 % CI, 1.56-5.51). Ten years of aging was associated with AAC (OR, 1.64; 95 % CI, 1.35-1.93), representing a 4.6- and 3-fold lower risk compared with being a current or former smoker, respectively. After 4 years of follow-up, both current and former smoking were associated with AAC progression (OR, 2.57; 95 % CI, 1.08-6.14; and OR, 2.34; 95 % CI, 1.07-5.13, respectively). Heavy smoking and longer smoking duration further increased this risk.

Conclusions: smoking status was associated with a higher prevalence and progression of AAC. In conclusion, smoking conferred a greater risk of AAC than aging itself.

Keywords: Aortic calcification. Smoker. Former smoker. Aging.

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INTRODUCTION

Cardiovascular diseases (CVDs) have been the leading cause of death since the early 20th century, representing a substantial burden on health care systems (1). Among cardiovascular conditions, atherosclerosis has traditionally been the primary underlying cause. Early identification of individuals at high risk of developing atherosclerosis is essential to prevent disease progression (2). Abdominal aortic calcification (AAC) is considered a key marker of atherosclerosis and an independent predictor of cardiovascular morbidity and mortality (3). Previous studies indicate that severe AAC is associated with an increased risk of cardiovascular events, reflecting impaired cardiovascular health (4).

Epidemiological studies indicate that CVD is a common process associated with aging, a nonmodifiable risk factor (5,6). However, numerous modifiable risk factors can accelerate physiological aging and contribute to the development of CVD. Among these, smoking is one of the most well-recognized contributors to atherosclerosis and other CVDs and represents a major public health problem (7,8). Globally, approximately 11 % of cardiovascular deaths are attributable to tobacco exposure (9). Although several studies have examined the relationship between aging or smoking and atherosclerotic events, evidence regarding the interaction between age and smoking in aortic calcification remains limited (10). A deeper understanding of this interaction may provide new insights into atherosclerosis development and help identify individuals who may benefit most from smoking cessation programs.

This study hypothesized that the relationship between age and aortic calcification is strongly influenced by tobacco exposure in a representative sample of men aged > 50 years. Therefore, the objective was to assess the effect of smoking on the prevalence and progression of AAC in an unselected population of men older than 50 years.

MATERIALS AND METHODS

This study was based on data obtained from a substudy of the multicenter European Vertebral Osteoporosis Study (EVOS), which aimed to assess the prevalence of vertebral fractures (11). The Bone Metabolism Unit of the Clinical Management Unit of Internal Medicine at the Hospital Universitario Central de Asturias (Asturias, Spain) randomly selected a cohort of 306 men aged > 50 years. Participants completed a questionnaire covering various osteoporosis-related risk factors, including diabetes and smoking status, specifying age at smoking initiation, number of cigarettes smoked per day, and smoking duration. Former smokers were defined as individuals who had abstained from smoking for at least one year. Two lateral dorsolumbar radiographs were obtained to assess vertebral fractures and aortic calcifications. Anthropometric measurements (height and weight) were recorded to calculate BMI. All participants were ambulatory enough to climb 2 flights of stairs without an elevator, and 99 % lived independently in their own homes.

After 4 years, participants were invited to repeat the study, including new radiographic examinations, anthropometric measurements, and a second questionnaire on osteoporosis-related risk factors. Individuals receiving osteoporosis treatment were excluded from the analysis at follow-up. A total of 148 men participated in this 2nd phase.

Random selection of the general population was performed by age groups, with 50 individuals per group (50-54, 55-59, 60-64, 65-69, 70-74, and > 75 years), without applying inclusion or exclusion criteria. Although renal function was not considered during recruitment, follow-up revealed that only 9 % had an estimated glomerular filtration rate (eGFR) > 90 mL/min/1.73 m^2; most participants were classified as stage 2 (59.6 %), followed by stage 3a (26.3 %) and stage 3b (5.1 %). These findings are consistent with age-related renal impairment in a cohort with a mean age of 68 years. Lipid-lowering therapy and cardiovascular events were not recorded; diabetes was the only cardiovascular risk factor analyzed.

ASSESSMENT OF PREVALENCE AND PROGRESSION OF VASCULAR CALCIFICATION

AAC was assessed on radiographs by 2 independent investigators blinded to both AAC status and smoking history. AAC was classified into 3 grades:

- Grade 0: absent.
- Grade 1: mild to moderate.
- Grade 2: severe.

Mild-to-moderate AAC was defined as isolated punctate calcifications, a linear calcification involving fewer than 2 vertebral bodies, or a single dense calcified plaque. Severe AAC was defined as a linear calcification extending over at least 2 vertebral bodies and/or the presence of 2 or more dense calcified plaques. Inter- and intraobserver agreement was excellent, reaching 92 % and 90 %, respectively, with κ coefficients of 0.78 and 0.73, indicating high reproducibility (12).

AAC progression was defined as an increase in the extent of baseline aortic calcification or the appearance of new calcifications over the 4-year follow-up period.

All procedures were conducted in accordance with the Declaration of Helsinki and were formally approved by the Research Ethics Committee for Medicinal Products (CEIm) of the Principality de Asturias (Asturias, Spain).

STATISTICAL ANALYSIS

Statistical analyses were performed using SPSS version 25.0 for Windows. Quantitative variables were analyzed using the Student *t* test or the Mann-Whitney U test, depending on whether they followed a normal distribution. Categorical variables were analyzed using the chi-square test.

Multivariable logistic regression analyses were conducted to assess the association between smoking status and both the presence and progression of AAC, adjusting for age and BMI.

RESULTS

At baseline, 30.1 % of the study subjects were current smokers, 43.8 % former smokers, and 26.1 % never smokers. No significant differences were observed in BMI values or diabetes prevalence among these three groups; however, differences were found in age. Current smokers were the youngest group (63.9 ± 8.2 years), followed by never smokers (64.3 ± 9.4 years), whereas former smokers were significantly older (67.8 ± 8.8 years; $p < 0.05$ compared with each of the other two groups separately) (Table I). No differences were found in the age at smoking initiation between current and former smokers, which was approximately 17 years in both cases, nor in the number of cigarettes smoked, which averaged around one pack per day in both groups. When current and former smokers were analyzed together, it is noteworthy that 75 % of individuals who consumed more than 40 cigarettes per day had started smoking early, before the age of 15. In addition, among those who smoked between 21 and 40 cigarettes per day, nearly half initiated smoking between 15 and 19 years of age.

Regarding smoking duration, the number of years of smoking was significantly higher among current smokers, with a mean of 46.0 ± 9.9 years, compared with 36.5 ± 12.8 years in former smokers ($p = 0.007$) (Table I). Current and former smokers showed a higher prevalence of AAC (52.7 % and 52.6 %, respectively) than never smokers (25 %; $p < 0.001$) (Fig. 1). AAC progression was also significantly higher in current and former smokers (61.0 % and 58.7 %, respectively) compared with never smokers (37.8 %; $p = 0.032$) (Fig. 1).

Differences were also observed in AAC prevalence according to the degree of clinical involvement (mild-moderate vs severe) across smoking status groups. The prevalence of mild-moderate AAC was significantly higher in current smokers (28.6 %) and former smokers (25.6 %) than in never smokers (17.5 %; $p = 0.012$ and $p = 0.020$, respectively). These differences were even more pronounced for severe AAC, whose prevalence was considerably higher in current smokers (24.2 %) and former smokers (27.1 %) compared with never smokers (7.5 %; $p = 0.001$ and $p < 0.001$, respectively). After adjusting for variables such as age and BMI, smoking status remained significantly associated with AAC prevalence. Being a current smoker was associated with AAC prevalence (odds ratio [OR] = 3.95; 95 % confidence interval [95 % CI], 2.00-7.82), an association also observed in former smokers (OR, 2.93; 95 % CI, 1.56-5.51). In addition, each 10-year increase in age was associated with a 64 % increase in AAC prevalence (OR, 1.64; 95 % CI, 1.35-1.93), representing an association approximately 4.6 times weaker than that observed in current smokers and 3 times weaker than that observed in former smokers. Inclusion of diabetes in the multivariate model did not modify these results.

Cumulative tobacco consumption, expressed as pack-years, and its association with AAC prevalence and progression are shown in table II. Compared with never smokers, cumulative tobacco consumption cat-

Table I. Demographic and smoking habit variables

Variables	Current smoker (*n* = 92)	Former smoker (*n* = 134)	Never smoker (*n* = 80)
Age (years)	62.9 ± 8.2	*67.8 ± 8.8*[ab]	64.3 ± 9.4
BMI (kg/m^2)	26.8 ± 3.6	27.0 ± 3.0	27.3 ± 3.5
Diabetes, *n* (%)	6 (6.5 %)	16 (11.9 %)	5 (6.2 %)
Habit onset (years)	16.7 ± 5.9	17.4 ± 5.7	-
Habit cessation (years)	-	54.1 ± 12.0	-
Smoking duration (years)	*46.0 ± 9.9*[a]	36.5 ± 12.8	-
Number cigarettes/day	19.0 ± 12.8	22.0 ± 14.3	-

[a]p *< 0.05 vs never smoker;* [b]p *< 0.05 vs current smoker.*

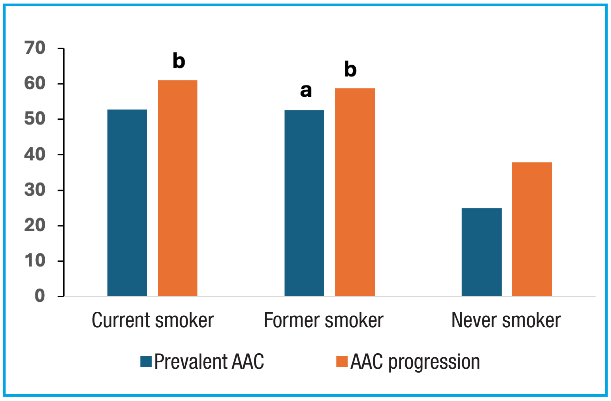

Figure 1. Proportion of men with prevalent AAC and AAC progression according to smoking status. $^{a}p < 0.01$, $^{b}p < 0.05$ vs never smokers.

lence, with the highest association observed in tertile 3 (> 45.46 pack-years) (OR, 7.73; 95 % CI, 3.65-16.38). Both tertile 2 (26.58-45.46 pack-years) and tertile 1 (<2 6.58 pack-years) were also associated with AAC prevalence (OR, 2.44; 95 % CI, 1.19-5.01 and OR, 2.73; 95 % CI, 1.33-5.61, respectively).

To provide an alternative perspective on total tobacco exposure, smoking was dichotomized according to the number of cigarettes smoked per day and duration of smoking. The effect of the number of cigarettes smoked per day on AAC prevalence is particularly noteworthy (Table III). Using never smokers as the reference group, logistic regression analysis adjusted for age and BMI showed that smoking more than 40 cigarettes per day was associated with an almost 12-fold increase in AAC risk (OR, 11.95; 95 % CI, 2.78-51.29). To a lesser but still statistically significant extent, smoking 20-39 cigarettes per day was associated with more than a fourfold increase in AAC risk (OR, 4.43; 95 % CI, 1.97-9.94), a value similar to that observed for smoking 11-20 cigarettes per day (OR, 3.72; 95 % CI, 1.89-7.32). Notably, even smoking 10 cigarettes or fewer per day was significantly associated with an increased AAC risk (OR, 2.62; 95 % CI, 1.23-5.59).

Smoking duration also had a substantial impact on AAC risk (Table III). Using never smokers as the reference group, logistic regression analysis adjusted for age and BMI showed that current smokers, with a mean smoking duration of 46 years, had nearly a fourfold higher risk of AAC (OR, 3.88; 95 % CI, 1.96-7.64). Former smokers with more than 40 years of smoking exposure showed a similar AAC risk (OR, 4.14; 95 % CI, 1.90-9.03), whereas former smokers with 20-39 years of exposure had an almost threefold higher risk (OR, 2.69; 95 % CI, 1.29-5.57). In contrast, being a former smoker with less than 20 years of smoking exposure was not significantly associated with increased AAC risk (OR, 1.59; 95 % CI, 0.43-5.94) (Table III). It is also worth noting that only 8.3 % of former smokers with less than 20 years of smoking exposure had smoked more than 20 cigarettes per day, a proportion more than three times lower than that observed among those who had smoked for more than 20 years.

Given the relatively short follow-up duration of the cohort (4 years), one might expect a low probability of detecting an association between ever smoking and AAC progression. Nevertheless, analysis of the effect of smoking status on AAC progression showed that both current and former smoking were associated with greater AAC progression (OR, 2.57; 95 % CI, 1.08-6.14 and OR, 2.34; 95 % CI, 1.07-5.13, respectively), independent of age and BMI.

Total tobacco exposure in pack-years showed that the two highest tertiles were associated with greater AAC progression [(OR, 3.51; 95 % CI, 1.33-9.28) for tertile 3 and (OR, 2.69; 95 % CI, 1.04-3.99) for tertile 2] (Table II). The number of cigarettes smoked per day was also associated with AAC progression. Smoking more than 20 cigarettes per day was associated with a significant increase in the risk of AAC progression (OR, 3.51; 95 % CI, 1.49-8.00), similar to that observed among those smoking 11-20 cigarettes per day (OR, 3.09; 95 % CI, 1.08-8.81). In contrast, smoking 10 cigarettes or fewer per day was not associated with an increased risk of AAC progression (Table IV).

Table II. Association of cumulative tobacco consumption in pack-years with AAC prevalence in smokers and former smokers

Outcome	Covariate (pack-years)	Number	OR (95 % CI)
AAC prevalence	Tertile 3 (< 25.58)	71	*7.73 (3.65-16.38)*
	Tertile 2 (26.58-45.46)	70	*2.44 (1.19-5.01)*
	Tertile 1 (> 45.46)	69	*2.73 (1.33-5.61)*
	Never smoker	80	Reference
AAC progression	Tertile 3 (< 25.58)	31	*3.51 (1.33-9.28)*
	Tertile 2 (26.58-45.46)	31	*2.69 (1.04-6.95)*
	Tertile 1 (> 45.46)	31	1.61 (0.65-3.99)
	Never smoker	45	Reference

The reference value 1 refers to never smokers. Statistically significant associations are shown in italics.

Table III. Association of stratification of the number of cigarettes consumed per day and the number of years with smoking habit with AAC prevalence in smokers and former smokers

Covariate (cigarettes/day as a smoker)	Number	OR (95 % CI)
> 40 cigarettes/day	12	*11.95 (2.78-51.29)*
21-40 cigarettes/day	46	*4.43 (1.97-9.94)*
11-20 cigarettes/day	94	*3.72 (1.89-7.32)*
≤ 10 cigarettes/day	58	*2.62 (1.23-5.59)*
Never smoker	80	Reference
Covariate (number years as smoker)	**Number**	**OR (95 % CI)**
Current smoker (> 46 years smoking)	91	*3.88 (1.96-7.64)*
Former smoker with ≥ 40 years smoking	56	*4.14 (1.90-9.03)*
Former smoker with 20-39 years smoking	62	*2.69 (1.29-5.57)*
Former smoker with < 20 years smoking	13	1.59 (0.43-5.94)
Never smoker	80	Reference

The reference value 1 refers to never smokers. Statistically significant associations are shown in italics.

Table IV. Association of stratification of the number of cigarettes consumed per day and the number of years of smoking habit with AAC progression in smokers and former smokers

Covariate (cigarettes/day as smoker)	Number	OR (95 % CI)
> 20 cigarettes/day	23	*3.09 (1.08-8.81)*
11-20 cigarettes/day	47	*3.51 (1.49-8.30)*
≤ 10 cigarettes/day	27	0.97 (0.36-2.60)
Never smoker	45	Reference
Covariate (number years as smoker)	**Number**	**OR (95 % CI)**
Current smoker (> 46 years smoking)	41	*2.57 (1.08-6.14)*
Former smoker with ≥ 40 years smoking	17	*3.95 (1.18-13.19)*
Former smoker with 20-39 years smoking	37	1.65 (0.36-7.46)
Former smoker with < 20 years smoking	8	1.94 (0.80-4.69)
Never smoker	45	Reference

The reference value 1 refers to never smokers. Statistically significant associations are shown in italics.

Smoking duration was also associated with AAC progression. Both current smokers with more than 40 years of smoking exposure and former smokers with the same duration showed a higher risk of AAC progression (OR, 2.57; 95 % CI, 1.08-6.14 and OR, 3.95; 95 % CI, 1.18-13.19, respectively). However, although former smokers with less than 40 years of exposure showed increased AAC progression, this association was not statistically significant (Table IV), possibly due in part to the smaller number of participants in the follow-up study.

DISCUSSION

The results of this cohort of men older than 50 years showed that being a current or former smoker was associated with an approximately fourfold and threefold higher risk, respectively, of AAC prevalence compared with never smokers. Moreover, despite the relatively short follow-up of 4 years, both current and former smokers exhibited an approximately twofold higher risk of AAC progression compared with never smokers. In addition, cumulative tobacco exposure (pack-years), number of cigarettes smoked per day, and duration of smoking were key determinants of increased AAC prevalence and progression.

Former studies have reported associations similar to those observed in the present work, although most focused on prevalence, with very few analyzing AAC progression over time. A prevalence study conducted in a Japanese population aged 40-79 years showed that being a current smoker was associated with an AAC OR of 4.29, nearly identical to that observed in our study (OR, 3.95), although AAC was assessed using computed tomography rather than plain radiography. Very similar results were observed among former smokers in that study, with an OR of 2.55 (13), again close to the OR of 2.93 found in our work. Another study in a South Korean population aged 40-81 years also showed an association between current smoking and increased AAC prevalence (OR, 5.05), a value higher than that found in our study using computed tomography; however, the association was slightly lower among former smokers (OR, 2.10) (14).

Regarding AAC progression, our findings are consistent with those reported in the only available 5-year prospective study evaluating the association between smoking and AAC at the time this article was written. That study, conducted in a Japanese population aged 40-79 years using computed tomography, showed that being a smoker was associated with a 2.47-fold increased risk of AAC progression (15), almost identical to that observed in our study (OR, 2.57) with only 4 years of follow-up. Heavy tobacco exposure has also been shown to be a strong risk factor for AAC. The highest cumulative exposure (tertile 3, pack-years) was associated with increased AAC prevalence. These results are consistent with those reported by other authors using computed tomography, although with an OR (3.90) approximately half of that observed in our study. Differences in population age, race, and the inclusion of only current smokers may partly explain these discrepancies (13). It is also noteworthy that in our study, cumulative exposure in the higher tertiles (tertiles 2 and 3) was associated with AAC progression, whereas other authors did not observe this association (15), possibly due to differences in race and the younger age of the cohorts studied (40-79 years).

To further explore the effect of smoking, tobacco exposure was analyzed separately by number of cigarettes smoked per day and total duration of smoking. As shown in table III, AAC risk increased proportionally with the number of cigarettes smoked per day, reaching a 12-fold higher risk among those smoking more than two packs per day (> 40 cigarettes). Notably, even moderate consumption of 10 cigarettes or fewer per day was associated with a 2.5-fold higher AAC risk compared with never smokers. These findings are consistent with those reported by Jung et al. in a Japanese population (14), as well as with other studies (16,17).

Although tobacco smoke contains multiple substances potentially harmful to the cardiovascular system (18), the precise mechanisms linking smoking to CVD are not fully understood. Nicotine, carbon monoxide, and certain oxidizing agents have been implicated in processes related to cardiovascular health (19). Some studies have reported a relationship between smoking and impaired endothelium-dependent arterial dilation, as well as increased carotid intima-media thickness (20,21). Free radicals and nicotine present in tobacco smoke may also contribute to structural changes in blood vessels, although these effects may vary according to the intensity and duration of exposure.

As noted in the Results section, not only high daily cigarette consumption but also longer smoking duration contributed to increased AAC risk, with the exception of former smokers with less than 20 years of exposure, in whom no association with AAC prevalence was observed. Other authors have similarly reported that smoking duration longer than 20 years was associated with an OR of 5.28 for AAC prevalence (14), consistent with our findings, where smoking for 20-40 years was associated with an OR of 4.43, increasing to 11.95 among those with more than 40 years of exposure. Some studies have also suggested that the association between smoking and AAC risk diminishes with longer smoking cessation (13). Lv et al. showed that quitting smoking for more than 10 years may partially attenuate the damage caused by tobacco exposure (22). These findings confirm that smoking is a powerful risk factor for CVD and that its harmful effects increase with both duration and intensity of exposure (23,24). Therefore, health care professionals should be aware that there is no safe level of smoking. Promoting abstinence, beyond merely reducing consumption, should be a priority in medical care, even when patients' symptoms are not directly related to cardiovascular system disorders. Smoking cessation remains one of the most effective interventions for reducing the long-term risk of cardiovascular events.

In Spain, most smokers begin smoking during adolescence or early adulthood, meaning that individuals with more than 20 years of exposure are often at an age when chronic diseases such as metabolic syndrome begin to emerge, accelerating atherosclerosis (25). Atherosclerosis is a slow, age-related process (26), and smoking acts as a major accelerator of vascular deterioration, promoting calcification in structures such as the abdominal aorta (27-29). Although postmortem studies have shown early atherosclerotic changes even in young individuals, radiologic detection of calcifications typically occurs at more advanced stages (30,31). Thus, our results highlight the need to reinforce preventive medical counseling, particularly among middle-aged and older patients with long-term smoking exposure or those who continue to smoke. It is essential to address not only the general health effects of smoking but also its relationship with vascular calcification and cardiovascular risk.

Although smoking cessation may slow the progression of atherosclerosis, vascular events, and possibly calcification, it is unlikely to reverse established calcification in smokers with heavy cumulative exposure. In moderate former smokers, quitting at an early age may delay or prevent this process, with benefits increasing with longer cessation duration (32).

Age is a well-established risk factor for CVD and specifically for AAC (12). In the present study, each 10-year increase in age was associated with a 60 % higher AAC risk. However, this risk was 4.6 and 3 times lower than that associated with current and former smoking, respectively, underscoring the importance of preventive interventions aimed at smoking cessation regardless of population aging.

Despite the findings obtained, the present study has several limitations. The study design was observational and prospective, which does not allow the observed associations to be interpreted as causal relationships. However, cumulative exposure expressed as cigarettes per day and duration of smoking provides information on both past and current exposure, suggesting a possible causal relationship. Another potential limitation is the lack of statistical handling of losses to follow-up. We cannot rule out as a likely limitation that the primary outcome of this cohort was not AAC but vertebral fracture. Nevertheless, given the strong association between fragility fractures and vascular calcification, this limitation may be partially mitigated. On the other hand, the use of plain radiography is a much less sensitive technique than computed tomography. However, comparisons between the diagnosis of vascular calcification and arterial plaques using these techniques have shown that X-ray assessment remains a reliable marker of vascular calcification and cardiovascular disease, being comparable in usefulness to techniques such as carotid intima-media thickness measurement (33,34), while also offering the advantage of greater availability and accessibility in clinical practice. Finally, although some of the main known confounding factors were carefully controlled for, it is possible that the results of this study were partially influenced by differences in unmeasured confounders, such as the presence of cardiovascular risk factors or the use of lipid-lowering therapies, which may have led to an overestimation of the observed associations. In fact, the highest cumulative tobacco exposure (tertile 3) remained associated with AAC progression, although more modestly, decreasing from (OR, 3.51; 95 % CI, 1.33-9.28) to (OR, 2.95; 95 % CI, 1.05-8.25) when AAC prevalence and estimated glomerular filtration rate—this latter covariate collected only at follow-up—were added to age and BMI as covariates. All these limitations, together with a small sample size such as ours, may have limited the strength of the associations observed.

Nevertheless, despite these limitations, the results have important clinical and public health implications, as lateral dorsolumbar spine radiography could be used to determine AAC in these higher-risk patients. This technique is a simple, inexpensive, and commonly performed test in clinical settings and during routine health examinations; however, AAC is often overlooked. In conclusion, the results of this study allow us to conclude that being a current or former smoker was significantly associated with a higher risk of AAC prevalence and progression. Even moderate daily consumption of < 10 cigarettes increases the risk of AAC by 2.5-fold compared with never smokers. Smoking as a risk factor showed a stronger association than aging per se. Therefore, given the increasing burden of cardiovascular disease and the continued prominence of smoking, the detection of AAC may represent an important early indicator of severe atherosclerosis and possibly other adverse effects among smokers, and should serve as a strong warning signal to recommend smoking cessation.

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Special Article

The parathyroid glands — Two centuries of research at the service of clinical practice

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Abstract

The discovery of the parathyroid glands and, years later, their therapeutic potential represents an outstanding example in the history of medicine of the role of basic research in shaping clinical practice. It is an excellent example because it is a subject that has been marked by conflicting interpretations, controversies, and failed trials, until reaching the point where, in 2002, the U.S. Food and Drug Administration (FDA) approved the use of the 1-34 fragment of human parathyroid hormone (hPTH) for the treatment of osteoporosis in men and postmenopausal women at high risk of fracture. From that moment onward, its use became widespread and consolidated in routine clinical practice. However, reaching this point was far from straightforward.

Over nearly 200 years, through successive observations carried out both in the laboratory and in the clinical setting, it has been possible to achieve a comprehensive understanding of the true function of an organ that was initially poorly understood. In this paper, I aim to briefly explain and review the most significant historical milestones in the understanding of the parathyroid glands and their hormone, as well as their subsequent clinical application.

This chapter in the history of medicine deserves to be remembered, as it clearly illustrates the collective learning process and how the accumulation of observations, followed by reflection, debate, and constructive discussion, leads to deeper knowledge of phenomena and realities that were previously little known or entirely unknown. Knowledge from which—clearly demonstrated in this example and readily extrapolated to many others—society ultimately always benefits.

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Parathyroid glands.
Hyperparathyroidism.
Hypercalcemia.
Parathyroid hormone.

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The parathyroid glands are small structures approximately 4 mm in diameter, usually located on the posterior aspect of the thyroid gland. The term used to define them is not entirely precise, as they may occasionally be intrathyroidal or extrathyroidal and can even be found far from the thyroid region, such as in the mediastinum. Perhaps for this reason, they were among the last organs to be discovered. Richard Owen (Fig. 1) was the first to identify them in 1850, not in humans but in a rhinoceros during an autopsy performed at the London Zoo (1). The existence of parathyroid glands in other mammals and in humans was established 30 years later, largely thanks to the work of Rudolf Virchow and Ivar Viktor Sandström (2) (Fig. 2).

Figure 1. R. Owen 1804-1892 (Source: Wellcome Collection. Public domain).

Figure 2. R. Virchow 1821-1902 (Source: Karl Virchow. Photograph by J. C. Schaarwächter, 1891. Wellcome Library, London; CC BY 4.0).

Their true function, however, remained unknown for some time. For years, anatomists believed that these glands were merely remnants of embryonic thyroid structures without any specific function.

At the end of the 19th century, studies by the French physiologist Marcel Eugène Émile Gley (Fig. 3) helped clarify the possible role of these thyroid remnants. He observed that animals developed tetany and died after inadvertent removal of the parathyroid glands during thyroid excision (3).

Gley mistakenly attributed this phenomenon to the absence of the thyroid gland together with the presumed embryonic remnants. It would take another decade for the Austrian pathologist Jacob Erdheim (Fig. 4) to provide the missing information. Erdheim demonstrated that animals developed postoperative tetany after thyroidectomy only when all parathyroid glands were also removed (4). Based on this evidence, he concluded that tetany was due to the absence of the parathyroid glands.

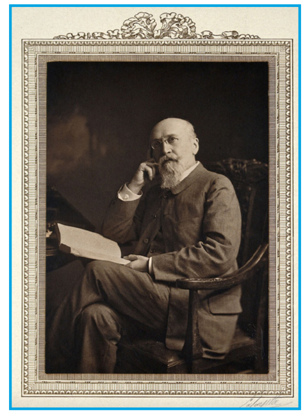

Figure 3. M. E. E. Gley 1857-1930 (Source: Wellcome Collection. Public domain).

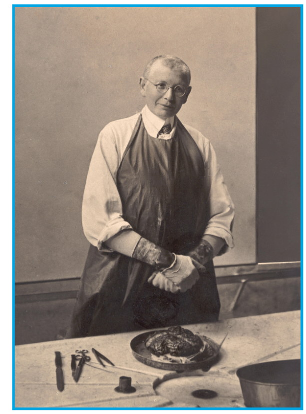

Figure 4. J. Erdheim 1874-1937 (Source: Jakob Erdheim, Wikipedia/Wikimedia Commons).

By that time, numerous studies had demonstrated the relationship between calcium salts and excitability of the central nervous system. William George MacCallum (Fig. 5) and Carl Voegtlin (Fig. 6) interpreted tetany as an expression of hyperexcitability and investigated the effects of calcium salts in this context. They observed that calcium infusions prevented tetany in parathyroidectomized animals. Thus, early in the 20th century, it became established that the metabolic alteration underlying tetany was hypocalcemia and that the function of the parathyroid glands was related to maintaining calcium homeostasis (5).

Nevertheless, the idea that tetany should be treated with calcium infusions had many detractors, sparking

Figure 5. W. G. MacCallum 1874-1944 (Source: Wellcome Collection. Public domain).

Figure 6. C. Voegtlin 1879-1960 (Source: Carl Voegtlin, Wikipedia/Wikimedia Commons).

an intense debate that lasted for decades. One reason for the controversy was that this approach conflicted with the emerging principle of organotherapy, which held that symptoms resulting from the absence of a gland should be reversed by administering extracts of that gland.

As a result, many researchers began administering infusions of parathyroid gland extracts prepared in their own laboratories. This approach was heavily criticized, partly with justification, as these preparations were not always as effective as calcium infusions. However, the controversy was resolved when the Canadian biochemist James Bertram Collip (Fig. 7) optimized extraction and purification techniques for parathyroid gland extracts (6) and demonstrated that these preparations not only prevented tetany episodes but were also capable of controlling serum calcium levels in parathyroidectomized animals. From that point onward, the role of the parathyroid glands as direct regulators of calcium homeostasis was firmly established.

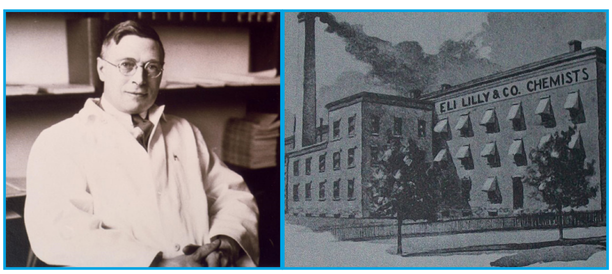

Figure 7. James Bertram Collip 1892-1965 (Source: J. B. Collip in his office at McGill University, ca. 1930, University of Toronto Library—scrapbook compiled by Barbara Collip Wyatt—Wikimedia Commons) and one of the buildings of the pharmaceutical company Eli Lilly & Co, originally opened in 1876 (Source: Eli Lilly and Company, 1886 newspaper advertisement. Public domain; Wikimedia Commons).

The relationship between the parathyroid glands and bone diseases was first documented in a commemorative volume written by thirteen of Virchow's disciples to celebrate his 70th birthday. Friedrich Daniel von Recklinghausen (7) (Fig. 8) devoted his chapter to describing autopsy findings in patients with bone disorders. He documented a case in which bone tissue had been replaced by fibrous tissue and cysts, a condition he termed osteitis fibrosa cystica (OFC). In the same case, he also described a reddish hypertrophic structure adjacent to the thyroid, which from today's perspective could correspond to a parathyroid adenoma. However, no hypothetical causal relationship was proposed at that time.

At the beginning of the 20th century, the most prevalent skeletal disease in Europe was osteomalacia due to vitamin D deficiency. European pathologists and anatomists were accustomed to performing routine autopsies on hospital patients, which explains the strong tradition of European schools of anatomical pathology. They observed that parathyroid glands were often enlarged in patients with fibrous and decalcified bone tissue. These findings led them to suspect a causal relationship, and given the contemporary perspective, they concluded that the glands were dysfunctional. They were unaware that parathyroid hypertrophy was a consequence of vitamin D deficiency rather than the cause of the disease.

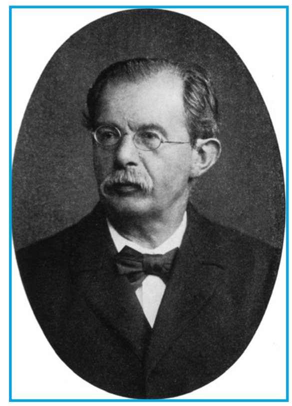

Figure 8. F. D. von Recklinghausen 1833-1910 (Source: Friedrich Daniel von Recklinghausen, Wikipedia/Wikimedia Commons).

Erdheim was perhaps the first pathologist to strongly suggest a relationship between the glands and bone disorders. He observed that some animals surviving the numerous parathyroidectomies performed in his laboratory developed dentin decalcification similar to that found in autopsies of patients with rickets (4). He therefore hypothesized that the presence of parathyroid glands was necessary for bone and dental growth. This idea raised many questions about the precise relationship between the parathyroid glands and osteomalacia, but the prevailing view at the time was that bone alterations were caused by glandular dysfunction and should therefore be treated with healthy parathyroid gland extracts.

However, the Austrian pathologist Friedrich Schlagenhaufer (1866-1930), based on autopsy findings from two patients with presumed "osteomalacia" (in fact OFC) who each had a single hypertrophic gland, challenged Erdheim's interpretation and that of his contemporaries (8). He proposed that the changes observed in the gland were the cause of the bone disease and that surgical removal would therefore be the appropriate treatment. Years later, and unintentionally, the Austrian surgeon Felix Mandl (1892-1957) (Fig. 9) demonstrated that Schlagenhaufer's theory was indeed correct (9).

Several more decades passed before the tireless reviews and observations of Fuller Albright (Fig. 10) established the distinction between two entities: osteomalacia in the context of secondary hyperparathyroidism and OFC typical of primary hyperparathyroidism (10). Indeed, at the beginning of the 20^{th} century, OFC was considered a variant of osteomalacia.

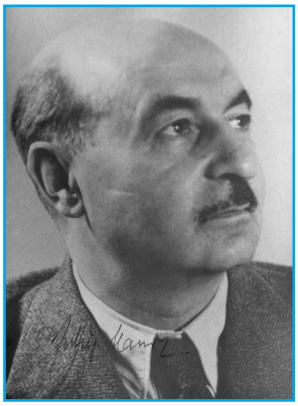

Figure 9. F. Mandl 1892-1957 (Source: Universität Wien—University of Vienna Archive, Felix Mandl (1892-1957), Surgery [Internet]).

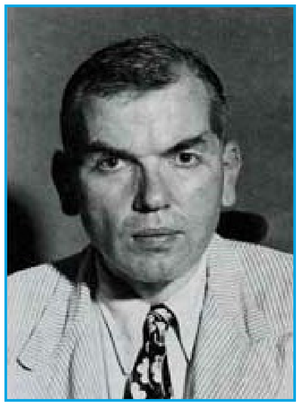

Figure10. Fuller Albright 1900-1969. (Source: Harvard Countway Library, A photograph of Fuller Albright, Wikipedia/ Wikimedia Commons).

Indeed, Mandl reached the same conclusion as Schlagenhaufer after treating a patient who would, over time, become an emblematic clinical case in the history of the parathyroid glands. It was 1924, and Dr. Mandl had assumed responsibility for the care of Mr. Albert Jahne, a tram driver who at that time had sustained a femoral fracture. However, the symptoms of the disease had begun 3 years earlier: generalized pain, fractures, bone cysts, demineralized bones, and elevated serum calcium. As was customary at the time, the case was interpreted in the context of dysfunctional parathyroid glands and, therefore, the patient received hormone extracts. When no satisfactory clinical changes were observed, Mandl transplanted glands from a cadaver, and when clinical deterioration nevertheless continued, he decided to explore the neck, where he indeed found a single hypertrophic gland. The surprise was that after its removal the patient improved dramatically (9). Mandl went down in history as the surgeon who performed the first therapeutic parathyroidectomy, and with this, Schlagenhaufer's thesis was also proven, namely that the cause of the skeletal disease resided in an adenomatous parathyroid gland.

Almost at the same time, across the Atlantic, in January 1926, a similar case arose that also became well known and symbolic in the medical literature. Dr. Eugene Floyd DuBois (1882-1959) received at Bellevue Hospital in New York City Charles Martell, a former captain of the United States Merchant Marine who had been experiencing progressive and disabling symptoms since 1919, which forced him to abandon his career four years later, in 1923. The patient also had elevated serum calcium. DuBois was aware of the investigations on phosphocalcic metabolism (11,12) being conducted in the newly created Pavilion No. 4 of Massachusetts General Hospital (Boston, MA, United States) (13). Physicians at Massachusetts General, especially Joseph Aub, had already used Collip's bovine parathyroid gland extracts to treat patients with lead poisoning (14). Aub had observed that injections of gland extracts caused hypercalcemia and hypercalciuria, and his idea was that this would induce not only the release of calcium bound to the bone matrix but also the release of lead. The connection between the parathyroid glands and hypercalcemia thus seemed more than plausible, and DuBois' provisional diagnosis was hyperfunctioning parathyroid glands (15).

It was the 1920s, and of course the exchange of knowledge between continents was not as fluid as it is today. Thus, the successful operation in Vienna was not yet known in the United States. In any case, even if it had been known, it would not have made any difference because Martell's adenoma was located in the mediastinum, an anatomic variation still unknown at that time (16).

Additional studies by Dr. Aub, Dr. Albright, and Dr. Bauer confirmed DuBois' diagnosis (17), and in May 1927 Captain Martell underwent the first neck exploration. However, no trace of an adenoma was found. Over the following years, while Martell slowly deteriorated, up to nine interventions were performed in a futile search for a parathyroid adenoma. It was then, some years later, when news arrived from Europe about the missing anatomic detail: the finding of a parathyroid tumor in the mediastinum at autopsy in a patient with osteitis fibrosa. Thus, in 1932, after his ninth surgery, the cause of Martell's disease was identified: a small adenoma in one of the parathyroid glands located in the thoracic cavity.

Captain Martell thus became another representative clinical case in this history of clinical discoveries, and without intending it, emerged from anonymity thanks to the efforts of the physicians and researchers of the time.

Of note, the differences in how investigators on the two continents approached the understanding of the disease. While in Europe this approach arose from anatomic changes documented by pathologists, in America it was pursued starting from observation of phosphocalcic metabolism and clinical presentation (13).

In the first quarter of the 20^{th} century, goiter due to iodine deficiency was endemic in the US region of Indiana. Many thyroidectomies were performed there, so the incidence of hypoparathyroidism and secondary hypocalcemia was frequent.

A local pharmaceutical company, Lilly, became interested in Collip's preparations (parathyroid gland extracts) with the commercial aim of treating hypocalcemia in some patients undergoing thyroidectomy. Thus, Lilly participated in the development of PTH extract production, which facilitated availability and represented an advantage for physiologists and investigators in the field, who quickly became interested in directly analyzing the effects of these extracts on the skeleton of animals.

In the 1930s, Hans Selye (Fig. 11) reported that Collip's extracts did not always induce bone resorption but, under certain conditions, could also induce bone formation in the rat skeleton (18,19). However, this observation fell into oblivion for 40 years. The reasons are unclear, but one possible explanation lies in the nature of these extracts, which, although they contained many active products, still retained impurities that made them insufficiently stable.

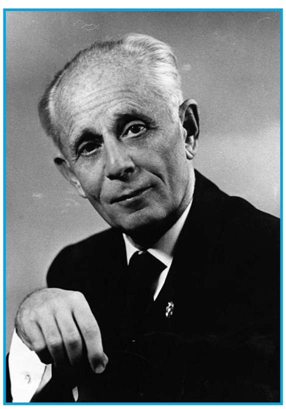

Figure 11. H. Selye (Source: Jean Paul Rioux, Portrait Hans Selye [Wikimedia Commons, CC BY-SA 4.0], 1907-1982).

Selye's idea, however, was revived by J. A. Parsons and B. Reit almost 50 years ago, in 1974 (20). While analyzing the serum calcium response in dogs treated with different doses of PTH, they observed, on the one hand, that low doses of PTH increased calcium absorption without inducing hypercalcemia and, on the other, that histologic sections of these animals' bones showed no increase in osteoclast number. Both observations led them to think that PTH might exert different actions on bone depending on the mode of administration, and that it did not always behave as an osteodestructive agent.

From that point onward, many investigators began studies on the actions of hormone fragments in the skeleton of animal models, allowing deeper understanding of these newly appreciated effects of the protein on bone. Thus, by the end of the 1960s, a preliminary clinical trial was justified to assess the reproducibility of these findings in humans (21).

Early clinical trials focused, among other aspects, on histomorphometric analysis of bone biopsies before and after receiving PTH fragments (22). In light of the results, the authors concluded that the drug could be useful in patients with osteoporotic fractures. Subsequently, antifracture efficacy studies were conducted (23), after which the drug began to be used clinically following its approval by the European Medicines Agency in 2003.

All of these studies conducted throughout the 1980s, and up to publication of the pivotal trial (23), generated great enthusiasm within the specialized scientific community. However, some skepticism remained about their true significance, and some clinicians—familiar with the devastating skeletal consequences of primary hyperparathyroidism—found it difficult to assimilate this paradigm shift.

Parathyroid hormone stimulates bone resorption (Fig. 12) but also bone formation (Fig. 13). What happens is that, depending on the mode of administration, one set of effects may predominate over the other, so that the net result can be more destructive than formative, or vice versa. When administration is continuous, as occurs in primary hyperparathyroidism, resorptive effects predominate. The underlying mechanism is explained by the fact that PTH, through its receptors on osteoblastic lineage cells, stimulates the expression of receptor activator of nuclear factor κB ligand (RANKL), a protein necessary and sufficient to induce osteoclast differentiation (24). However, intermittent administration of PTH attenuates RANKL expression, resulting in less striking resorption than in the continuous-administration scenario. In addition, intermittent administration increases the osteoblast pool and consequently bone formation. Through its receptor on mesenchymal cells, PTH promotes differentiation toward osteoblasts and, at the same time, decreases their capacity to differentiate into adipocytes (25,26). Furthermore, it attenuates apoptosis of osteoblasts and osteocytes (27) and activates quiescent osteoblastic lining cells on the bone surface, inducing their dedifferentiation into active osteoblasts capable of resynthesizing matrix (28).

PTH also acts on certain genes expressed specifically in osteocytes. In particular, it is a potent inhibitor of SOST expression, a gene encoding sclerostin, an antagonist of canonical WNT pathway signaling and, therefore, a strong inhibitor of bone formation. However, intermittent PTH administration does not reduce sclerostin levels as much as continuous administration, suggesting that this mechanism does not substantially contribute to the increase in osteoblast number resulting from daily PTH injections (29). What seems possible is that small transient decreases in sclerostin secretion after each PTH injection cause bursts of signaling that contribute to stimulating osteoblastogenesis, although, as noted, this is not the principal mechanism in this scenario.

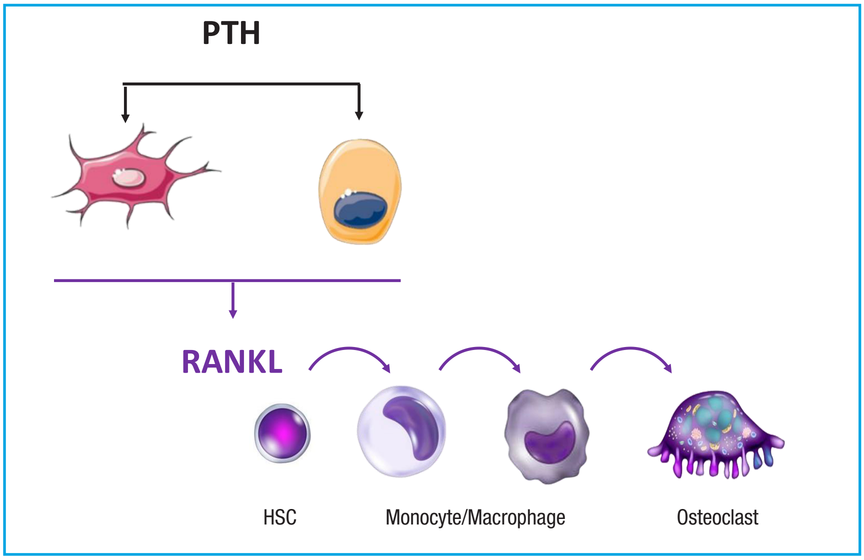

Figure 12. Effect of PTH on osteoclast differentiation: PTH stimulates RANKL expression in osteoblastic lineage cells. RANKL is a protein necessary and sufficient to stimulate osteoclast differentiation from the hematopoietic stem cell.

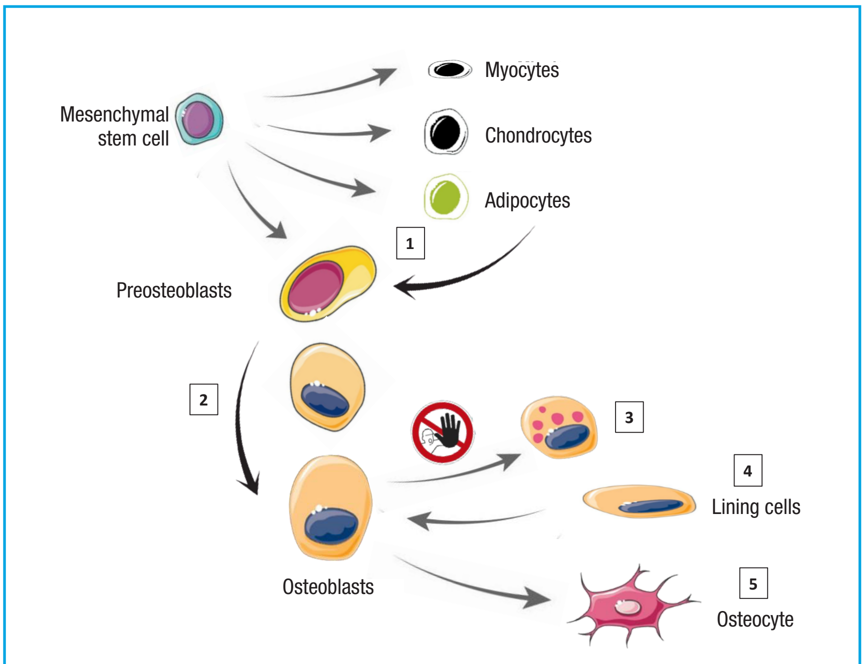

Figure 13. Effect of PTH on osteoblastic lineage cells: (1) prevents differentiation into adipocytes; (2) promotes preosteoblastic differentiation into osteoblasts; (3) inhibits osteoblast apoptosis; (4) reactivates lining cells, transforming them into osteoblasts; (5) inhibits SOST expression in osteocytes.

Histologic studies indicate that during the first 10 months after initiating intermittent PTH there is an increase in osteoblast number and bone formation rate without an increase in osteoclast number, clearly providing a therapeutic window in which the desired anabolic effects are achieved (30). The molecular and cellular mechanisms by which PTH increases osteoblast number, as well as those contributing to the anabolic effect of intermittent administration, have thus been partially clarified over the last 20 years.

PTH exerts its effects through binding to the type 1 PTH receptor (PTH1R), located on the cell membrane. PTH1R is a member of the class B family of G protein–coupled receptors. It is expressed mainly in the skeleton and kidneys, where it regulates skeletal development, bone turnover, and calcium and phosphate homeostasis, but it is also expressed in the mammary gland and vascular wall smooth muscle (31). PTH is not the only endogenous ligand capable of triggering its activation. The other ligand is PTH-related protein (PTHrP), a polypeptide with three isoforms of 139, 141, and 173 amino acids. Unlike PTH, which is secreted by the parathyroid glands and has endocrine actions on distant organs, PTHrP is secreted by a wide variety of tissues and acts in a paracrine manner to regulate cellular differentiation and proliferation within the tissues from which it is secreted, mainly the chondral growth plate and the mammary gland (32-34). A synthetic ligand analogous to PTHrP also exists, consisting of 34 amino acids, of which ten at the carboxy-terminal end differ from the original endogenous molecule. This ligand is abaloparatide (ABL), which was approved by the FDA in 2017 as an osteoanabolic agent for the treatment of osteoporosis (35).

All ligands share similarities in the first 34 residues of the amino-terminal domain through which they bind to PTH1R. Ligand binding to PTH1R at the cell surface induces receptor changes that initiate coupling and activation of heterotrimeric G proteins (Gα, Gβ, and Gγ), followed by activation of multiple intracellular signaling cascades (32). The interaction of PTH1R with Gs stimulates activation of adenylyl cyclase, the enzyme that generates the second messenger cyclic adenosine monophosphate (cAMP). cAMP activates protein kinase A (PKA), which in turn activates several transcription factors, including cAMP response element-binding protein (CREB). This enables its nuclear translocation and binding to response elements in its target genes (36,37). PKA also phosphorylates and thereby inhibits a type of salt-inducible kinases (SIKs), which leads, on the one hand, to dephosphorylation of their substrates—class IIa histone deacetylases (HDACs) and cAMP-regulated transcriptional coactivators (CRTCs) (38)—and, on the other hand, facilitates their nuclear translocation (Fig. 14).

Activation of PKA and inhibition of SIK activity by PTH have been shown to be essential for the regulation of genes expressed in osteoblastic lineage cells. Class IIa HDAC4 and HDAC5 block expression of the osteocyte-specific SOST gene by inhibiting myocyte enhancer factor 2C (MEF2C). On the other hand, CRTC2 stimulates CREB-driven expression of receptor activator of nuclear factor κB ligand (RANKL).

Several studies have shown that PTH1R has 2 distinct high-affinity conformations: the R0 conformation, which is G protein-independent, and the RG conformation, which is G protein-dependent. Thus, ligand affinity for receptor conformations triggers cAMP signaling responses that differ in intracellular duration (39,40).

All ligands stimulate a transient increase in cAMP production from the cell surface. However, those that preferentially associate with the R0 receptor conformation induce a more sustained production derived from a second phase of cAMP generation. This occurs when the ligand–receptor–β-arrestin complex is internalized through endosomes and remains in the cytoplasm (41,42).

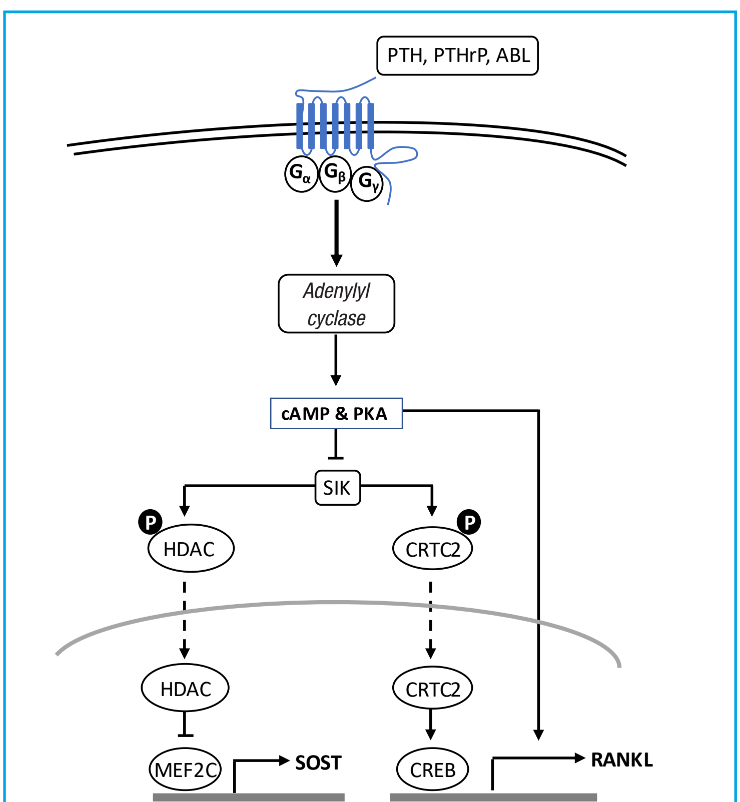

Figure 14. Model of intracellular signaling of PTHR1 and activation of gene expression. Scheme based on a figure published at https://doi.org/10.1038/s41574-024-01014-7.

All PTH1R ligands (PTH, PTHrP, and ABL) show similar binding affinity for the RG conformation, whereas affinity for the R0 conformation differs: it is greatest for PTH, followed by PTHrP, and then ABL. Despite the fact that ABL and PTH have similar affinity for the RG conformation and that ABL has the lowest affinity for the R0 conformation, ABL is the ligand that induces the most transient intracellular cAMP response compared with the other ligands (41-43).

This difference in ligand binding preference for one or the other PTH1R conformation, and the duration of cytoplasmic cAMP activity, could explain the differences observed between ABL and teriparatide (TPTD) in clinical models. In this regard, in the pivotal ACTIVE trial (Abaloparatide Comparator Trial in Vertebral Endpoints), which compared the effects of ABL and TPTD, the resorption marker C-terminal telopeptide of type I collagen (CTX) remained elevated throughout the 18 months of the study in the TPTD arm, whereas its increase was much more modest in the ABL arm (44).

It seems that the fleeting cAMP signaling induced by activation of the RG conformation of PTH1R is sufficient to ensure osteoforming effects and that, in this situation, RANKL expression is more limited, translating into a more modest resorptive action than when the R0 receptor conformation is activated. Therefore, this difference in binding preference for one or the other receptor conformation may explain why the overall anabolic action of ABL appears to be somewhat more pronounced than that of the other ligands.

In any case, what is fascinating about this history of discoveries—especially from a biological standpoint—is the realization that the same substance can have opposing effects depending on the mode of administration. We can conclude by noting that a long time has passed since Owen discovered the parathyroid glands in a rhinoceros. Since then, many scholars in their respective fields—anatomists, pathologists, physiologists, clinicians, and laboratory investigators—have contributed their effort and curiosity so that today we can use fragments of the hormone for therapeutic purposes. The road has been long, but it has been worth it.

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Case Report

The dark side of wrist fractures

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Resumen

Introduction: distal radius fracture is one of the most common reasons for consultation in rehabilitation and mainly affects elderly women.

Case report: we present the clinical case of a 78-year-old woman with a slow-healing distal radius fracture. After a detailed medical history and examination, reflex sympathetic dystrophy is suspected. Speckled osteoporosis was observed on plain wrist radiography, as well as laboratory abnormalities (hypovitaminosis D) and densitometric abnormalities (osteopenia in the femur/osteoporosis in the spine).

Discussion: the goal of rehabilitation treatment is to achieve maximum functionality of the affected limb, accelerate recovery, and prevent complications such as joint stiffness and pain. There are nosological entities that may initially go unnoticed, leading to an unfavorable clinical course. Early diagnosis and treatment are essential to minimize complications and long-term sequelae.

Keywords:
Distal radius fracture. Complex regional pain syndrome. Reflex sympathetic dystrophy. Early treatment. Osteoporosis.

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INTRODUCTION

Distal radius fracture (DRF) is a metaphyseal fracture that occurs in the distal 3 to 5 cm of the radius and primarily affects active and functionally independent adults. It is considered the second most frequent fracture, second only to hip fractures, and the most prevalent upper limb fracture in adults. According to sex, from the age of 65 years onward, women are 85 % more likely to sustain a DRF than men (1). According to the literature, DRFs account for 17.5 % of all fractures (2).

Stability is a critical parameter that dictates not only the immediate course of treatment but also the long-term prognosis of these fractures. Treatment of DRFs may be non-surgical, recommended for nondisplaced or stable fractures, whereas unstable or displaced fractures usually require surgical intervention. Treatment choice should be individualized, considering patient comorbidities and fracture characteristics, in order to ensure optimal and effective recovery (3).

Complex regional pain syndrome (CRPS) has received numerous designations, such as "algodystrophy," "algoneurodystrophy," "causalgia," or "Sudeck dystrophy," terms that are still used to refer to this frequent complication occurring in patients recovering from a DRF, with a reported incidence of up to 37 %. This condition is defined by the distal manifestation of a triad of symptoms (sensory, autonomic, and motor) in the affected limb, and its diagnosis is nonspecific, with uncertain utility and value (4).

There is no specific test for the diagnosis of CRPS. Complementary tests such as infrared thermography, three-phase bone scintigraphy, bone densitometry, Doppler flow studies, magnetic resonance imaging, or other autonomic function tests—such as the quantitative sudomotor axon reflex test and the thermoregulatory sweat test—are commonly used to rule out differential diagnoses (5).

Despite its low sensitivity and specificity, plain radiography remains one of the most accessible and easily obtainable tests. It may show signs of heterogeneous bone demineralization in painful regions and can help exclude other musculoskeletal conditions (6).

CASE REPORT

A 78-year-old woman was referred from the Trauma Department to the Rehabilitation Clinic for a left distal radius fracture.

Personal history: no known drug allergies. Dyslipidemia and hypothyroidism. No previous surgical interventions. Regular pharmacological treatment: simvastatin and levothyroxine.

Baseline status: independent in activities of daily living, living at home with her husband, walking without assistive devices.

Current illness: the patient sustained a fall from standing height with forced dorsal flexion of the left hand and was diagnosed with a left distal radius fracture by the Trauma Service in the Emergency Department of her referral area. Initial management consisted of closed reduction and immobilization with a dorsal forearm splint, which after one week was replaced by a circumferential cast that was removed after 30 days. During this period, the patient used a sling, removing it only for hygiene purposes.

She attended the Rehabilitation Clinic referred from Traumatology two weeks after cast removal. She had initiated wrist exercises at home but reported severe functional limitation and pain, requiring analgesia with ibuprofen 600 mg every 12 hours.

Initial assessment scales:
- VAS: 9/10
- LANSS: 19/24 (Table I).

Initial physical examination:
- *Left wrist and hand:* edema of the wrist and hand; pain on palpation of the radial styloid and radiocarpal joint line. Active range of motion: palmar flexion 70°, dorsal flexion -20°, ulnar deviation absent, radial deviation absent, pronation 50 %, supination 20 %. Unable to make a fist; finger-to-palm distance 8 cm. Terminal lateral opposition to the second finger without digital dissociation. Vascular and neurological examination showed vasomotor changes, stiffness of metacarpophalangeal and interphalangeal joints, neuropathic pain (hyperalgesia and allodynia in the palmar/digital region) with digital stiffness. Passive mobility was limited and difficult to assess due to pain (Fig. 1).
- *Left elbow:* no edema or joint deformity; no pain on palpation. Active range of motion: flexion 130°, extension -40°, limited pronosupination (previously assessed).
- *Left shoulder:* pain in the anterolateral aspect of the shoulder. Active range of motion: flexion 100°, abduction 100°, internal rotation reaching the sacrum with difficulty, external rotation reaching the nape with anteriorized elbow; passive capsular end-feel.

Complementary tests:
- Plain radiograph of the left wrist, two projections: left distal radius fracture with intra-articular involvement, degenerative changes, and patchy osteoporosis (Fig. 2A).

Differential diagnosis:
After a detailed history and complete physical examination supported by complementary tests, in

Table I. LANSS scale: the LANSS scale is a simple and valid 7-item tool used to identify patients with neuropathic pain. Scores above 12 points indicate a probable presence of neuropathic pain. The maximum score is 24 points. Initial and final follow-up results of the scale in the described case are shown

	LANSS scale	Initial	Final
Pain questionnaire	1. Does your pain feel like an unpleasant and strange sensation on your skin? The following words might describe this sensation: pricking, tingling, pins and needles. • NO, I do not really feel my pain this way (0) • YES, I often have these sensations (5)	5	0
	2. Does the appearance of the skin in the painful area look different from normal? The following words might describe this sensation: redness, blotchy, mottled. • NO, my pain does not affect the color of my skin (0) • YES, I have noticed that pain makes my skin look different (5)	0	0
	3. Does your pain make your skin abnormally sensitive to touch? These unpleasant sensations may be provoked by lightly stroking the skin or by clothing. • NO, pain does not make the skin in that area more sensitive (0) • YES, my skin feels abnormally sensitive when I touch that area (3)	3	3
	4. Does your pain suddenly come on like electric shocks without any apparent reason? The fol-lowing words might describe this sensation: electric current, jolts, stabbing. • NO, I do not feel my pain that way (0) • YES, I often have these sensations (2)	2	0
	5. Does the temperature in the painful area feel different from usual? The following words might describe this sensation: heat, hot, burning. • NO, I do not really have these sensations (0) • YES, I often have these sensations (1)	1	0
Sensory testing	1. ALLODYNIA: examine the response to lightly stroking the skin with cotton wool over a non-painful area and the painful area. If the sensation is normal in the non-painful area but painful or unpleasant (tingling, nausea) in the painful area, the test is positive. • NO, normal sensations in both areas (0) • YES, allodynia presents only in the painful area (5)	5	5
	2. PAIN THRESHOLD: determine pinprick threshold by comparing the response to a 23-gauge needle mounted on a 2-mL syringe, gently applied to the skin in a non-painful area and a pain-ful area. If pressure is felt in the non-painful area but produces a different sensation in the painful area (e.g., no sensation or pressure only [high threshold], or very painful sensation [low threshold]), pain threshold changes are present. If the needle is not felt in either area, change the syringe to increase weight and repeat the test • NO, same sensation in both areas (0) • YES, changes in pain threshold present in the painful area (3)	3	0
Total		**19/24**	**8/24**

addition to the left distal radius fracture, conditions such as thrombophlebitis, cellulitis, lymphedema, peripheral or compressive neuropathies (thoracic outlet syndrome, carpal tunnel syndrome), and inflammatory, rheumatic, or infectious arthropathies were ruled out.

Diagnosis:

- There is no specific test for diagnosing CRPS; diagnosis is mainly based on the observation of signs and symptoms. In this case, the Budapest Criteria (Table II) for the diagnosis of complex regional pain syndrome type I were fulfilled (5).
- CRPS type I – left shoulder–hand syndrome secondary to left distal radius fracture.

Therapeutic approach:

- *Pharmacological treatment:* analgesia with naproxen/esomeprazole (500 mg/20 mg) every 12 hours was initially prescribed, together with a nucleotide complex enriched with vitamins (uridine 5-monophosphate 300 mg and cytidine 5-monophosphate 100 mg, vitamin B1 1.1 mg, vitamin B12 2.4 mg) administered orally, one tablet every 24 hours, to reduce pain, facilitate neuronal regeneration, and improve overall nervous system function.
- *Physiotherapy treatment:* motor kinesiotherapy was prescribed to improve the range of motion of the left shoulder, elbow, wrist, and hand.
- *Additional tests requested:* bone densitometry (DXA) and blood tests.

Evolution and results:
The patient underwent specific kinesiotherapy of the shoulder, elbow, wrist, and hand to improve upper limb function.

- *DXA:* osteopenia at the proximal femur (T-score -1.9) and osteoporosis at the spine (T-score -3.0) (Fig. 2 C1 and C2).
- *Blood tests:* complete blood count with erythrocyte sedimentation rate; serum biochemistry including calcium, phosphorus, alkaline phosphatase, liver transaminases, urea and creatinine, estimated glomerular filtration rate, TSH, and PTH were within normal ranges. Vitamin D (25-hydroxyvitamin D) level was 25.3 ng/mL.

Therapeutic adjustment:
Oral treatment with alendronic acid 70 mg weekly was added, together with calcium 600 mg plus 2000 IU of cholecalciferol in a single daily oral dose (one orodispersible tablet every 24 hours) to improve treatment adherence.

Figure 1. Complex regional pain syndrome (CRPS) type I following left distal radius fracture. Dorsal view of the affected limb with comparison to the contralateral healthy side (A), and palmar view of the affected limb (B).

Table II. Budapest diagnostic criteria for complex regional pain syndrome (adapted from cite 5)
1. Continuous pain, disproportionate to the inciting event.
2. At least one symptom must be reported in three of the following four categories:
• *Sensory:* hyperesthesia and/or allodynia
• *Vasomotor:* asymmetry of skin temperature and/or skin color changes and/or skin color asymmetry
• *Sudomotor:* edema and/or sweating changes and/or asymmetric sweating
• *Motor:* decreased range of motion and/or motor dysfunction (tremor, dystonia, weakness) and/or trophic changes (skin, hair, nails)
3. At least one sign must be present in two or more of the following four categories:
• *Sensory:* evidence of hyperalgesia (to pinprick) and/or allodynia (to light touch/thermal stimulation/deep pressure/joint movement)
• *Vasomotor:* evidence of skin temperature asymmetry > 1 °C and/or skin color asymmetry and/or skin color changes
• *Sudomotor:* evidence of edema and/or asymmetric sweating changes
• *Motor:* evidence of decreased range of motion and/or motor dysfunction (tremor, dystonia, weakness) and/or trophic changes (skin, hair, nails)
4. Exclusion of other diagnoses that could better explain the above signs and symptoms

The patient continued physiotherapy and treatment with bisphosphonate, calcium, and vitamin D, with good clinical and radiological evolution (Fig. 2B). At the 3-month follow-up from the first visit, scale outcomes were as follows:

- VAS: 2/10.
- LANSS: 8/24 (Table I).

Final physical examination:

- *Left wrist and hand:* mild pain at the radiocarpal joint line; no edema or sudomotor changes. Active range of motion: palmar flexion 70°, dorsal flexion 40°, ulnar deviation 20°, radial deviation 10°, pronation 95 %, supination 95 %. Able to make a fist including the thumb; digital opposition to the fourth finger with functional digital dissociation; persistent stiffness of interphalangeal joints in the final degrees of extension.
- *Elbow:* no deformities or tenderness; active range of motion: flexion 140° with hand reaching the shoulder, extension 0°, functional pronosupination.
- *Shoulder:* no tenderness; active range of motion: flexion 130°, abduction 130°, internal rotation to the waist, external rotation to the contralateral ear.

After the therapeutic approach, pain was reduced and a functionally adequate global range of motion of the left upper limb was achieved, allowing correct performance of basic and instrumental activities of daily living.

Finally, the patient was discharged from Rehabilitation with recommendations to continue the exercise program learned at home to maintain limb function. Adherence to therapy was emphasized, with continued follow-up of osteoporosis by her primary care physician. After three months of treatment with oral calcium and cholecalciferol at the prescribed dosage, serum 25-hydroxyvitamin D levels increased to 43.3 ng/mL.

DISCUSSION

It has been estimated that an initial DRF increases the risk of future fragility fractures by 86 % in the presence of osteoporosis (7).

CRPS is a complication of DRFs characterized by chronicity and progressive worsening of fracture-related symptoms, which may lead to significant functional disability in affected patients. Diagnosis of this condition is based on a thorough analysis of the clinical history and, most importantly, on a comprehensive physical examination (8).

Three-phase bone scintigraphy is a valuable imaging tool for the diagnosis of CRPS. When combined with a multimodal analgesic approach, it allows monitoring of disease progression and response to treatment (9).

With regard to the present case, according to certain international guidelines (Bone Health & Osteoporosis Foundation), our patient would already have been eligible for DXA assessment, as these guidelines recommend performing this test from the age of 65 years onward even in the absence of additional risk factors (10). However, according to the 2022 update of the SEIOMM guidelines, DXA is recommended when risk factors strongly associated with osteoporosis or fractures are present (11) (Table III). In this case, DXA complemented the assessment of the patient's bone status and constitutes a useful tool for subsequent follow-up and treatment adjustment. If the patient's FRAX score had been calculated prior to the fracture, it would have shown an 8.5 % risk of major osteoporotic fracture and a 2.9 % risk of hip fracture; therefore, antiresorptive treatment could already have been considered even before the fracture occurred. Moreover, calcium and vitamin D supplementation should certainly have been evaluated, even with vitamin D values close to 30 ng/mL (12).

Along with anti-inflammatory treatment, bisphosphonate therapy was added, as these agents have been shown to improve inflammatory signs and mobility, although dosage, treatment duration, and route of administration vary across studies (13). Although osteoporotic status is independent of post-fracture complications, weekly alendronic acid treatment may help address both conditions by inhibiting osteoclastic bone resorption (14).

Of note, the cutoff values considered normal for serum 25-hydroxyvitamin D levels vary slightly among guidelines. SEIOMM considers it appropriate to maintain serum levels > 25-30 ng/mL in patients receiving pharmacological treatment for osteoporosis. In patients with osteoporosis or high fracture risk, levels between 30 ng/mL and 50 ng/mL are recommended to ensure efficacy without additional risks (11). Our patient had levels between 25 ng/mL and 30 ng/mL; however, given her classification as high risk, it was necessary to maintain serum 25-hydroxyvitamin D levels > 30 ng/mL.

There is near-unanimous agreement, supported by guidelines such as those of the Spanish Society of Rheumatology (SER, 2018), that when initiating any antiresorptive therapy, adequate calcium and vitamin D supplementation should be ensured (1000-1200 mg/day of calcium and 800 IU/day of vitamin D). This supplementation is essential for two reasons: first, to prevent hypocalcemia induced by the antiosteoclastic effect of these drugs; and second, because the proven efficacy of antiresorptive treatments in fracture reduction depends on maintaining optimal calcium and cholecalciferol levels (15).

Considering the ambiguity in defining therapeutic targets for osteoporosis and the short follow-up period, a long-term management strategy aligned with the SEIOMM continuation algorithm has been proposed (11).

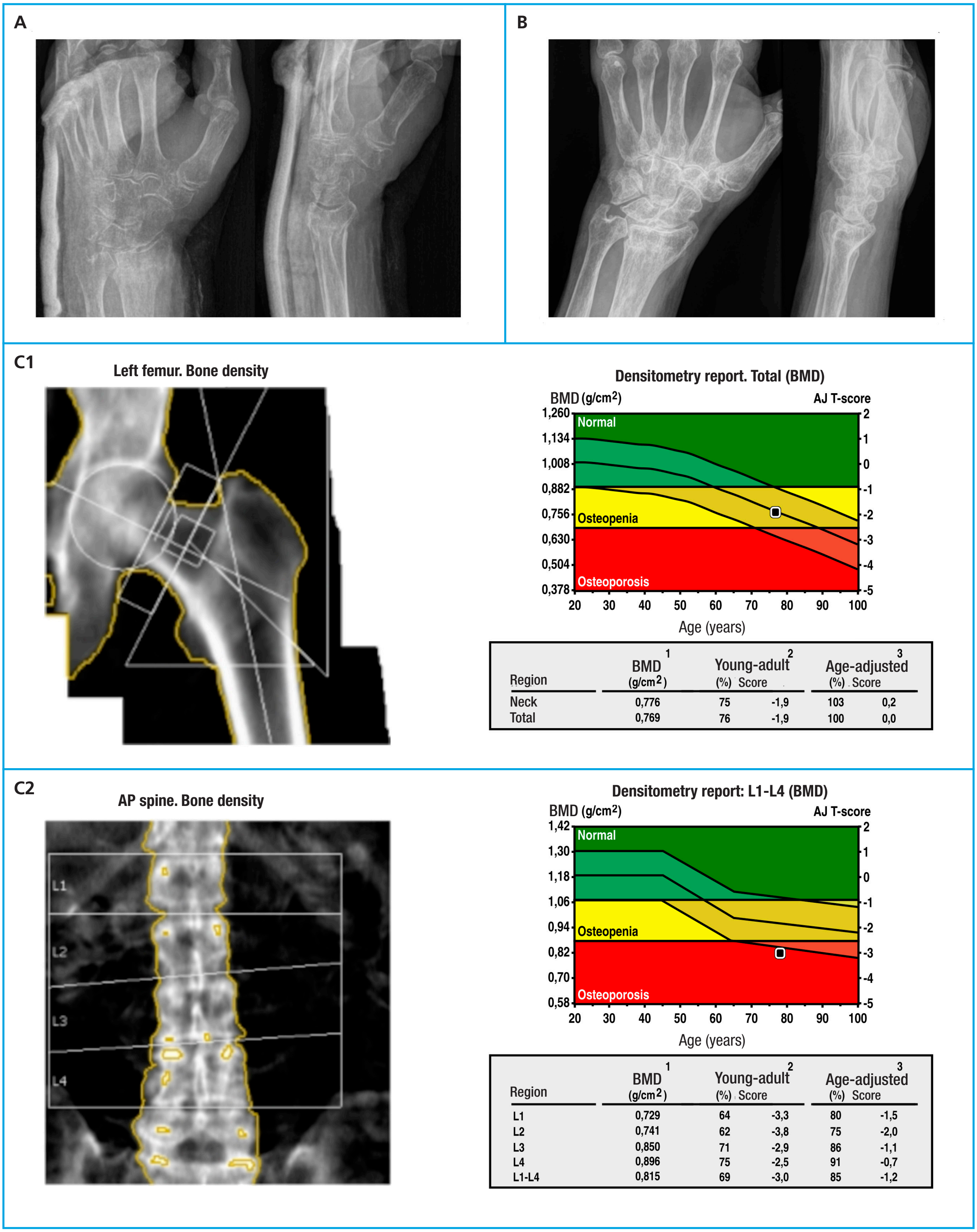

Figure 2. A. Plain radiograph of the left wrist, two projections, follow-up prior to removal of dorsal forearm plaster splint immobilization: distal radius fracture with intra-articular involvement, degenerative changes, and indirect signs of radiocarpal osteoporosis. B. Follow-up radiographic control after three months of treatment: consolidated distal radius fracture. C1. DXA: proximal femur results (osteopenia). C2. DXA: lumbar spine results (osteoporosis).

Table III. Risk factors for osteoporosis (11)
Factors clearly associated with osteoporosis
• Advanced age
• Female sex
• Personal history of fracture
• Family history of hip fracture
• Increased risk of falls
• *Diseases:*
– Hypogonadism
– Early menopause, amenorrhea
– Anorexia nervosa
– Malabsorption
– Rheumatoid arthritis
– Diabetes (particularly type 1)
– Immobilization
– Cushing disease
• *Treatments:*
– Glucocorticoids
– Aromatase inhibitors
– Gonadotropin-releasing hormone agonists (and other androgen deprivation therapies in men)
Other factors associated with less consistent evidence
• Hyperparathyroidism, hyperthyroidism
• Calcium deficiency
• Vitamin D deficiency
• *Drugs and toxins:*
– Selective serotonin reuptake inhibitors
– Proton pump inhibitors
– Anticonvulsants
– Antiretrovirals
– Alcohol, tobacco

This individualized strategy includes weekly alendronate administration together with calcium and vitamin D for a total of five years. Treatment will be monitored between the second and third year, and based on response and individual patient profile, the need to continue, interrupt, or switch therapy to other agents—such as the antiresorptive denosumab or the osteoanabolic agent teriparatide—will be determined.

Early, individualized, and multidisciplinary treatment—based on pharmacological pain control, rehabilitative therapy, and comprehensive assessment of the patient and associated comorbidities—is crucial to achieve the greatest possible functional recovery while minimizing long-term sequelae.

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