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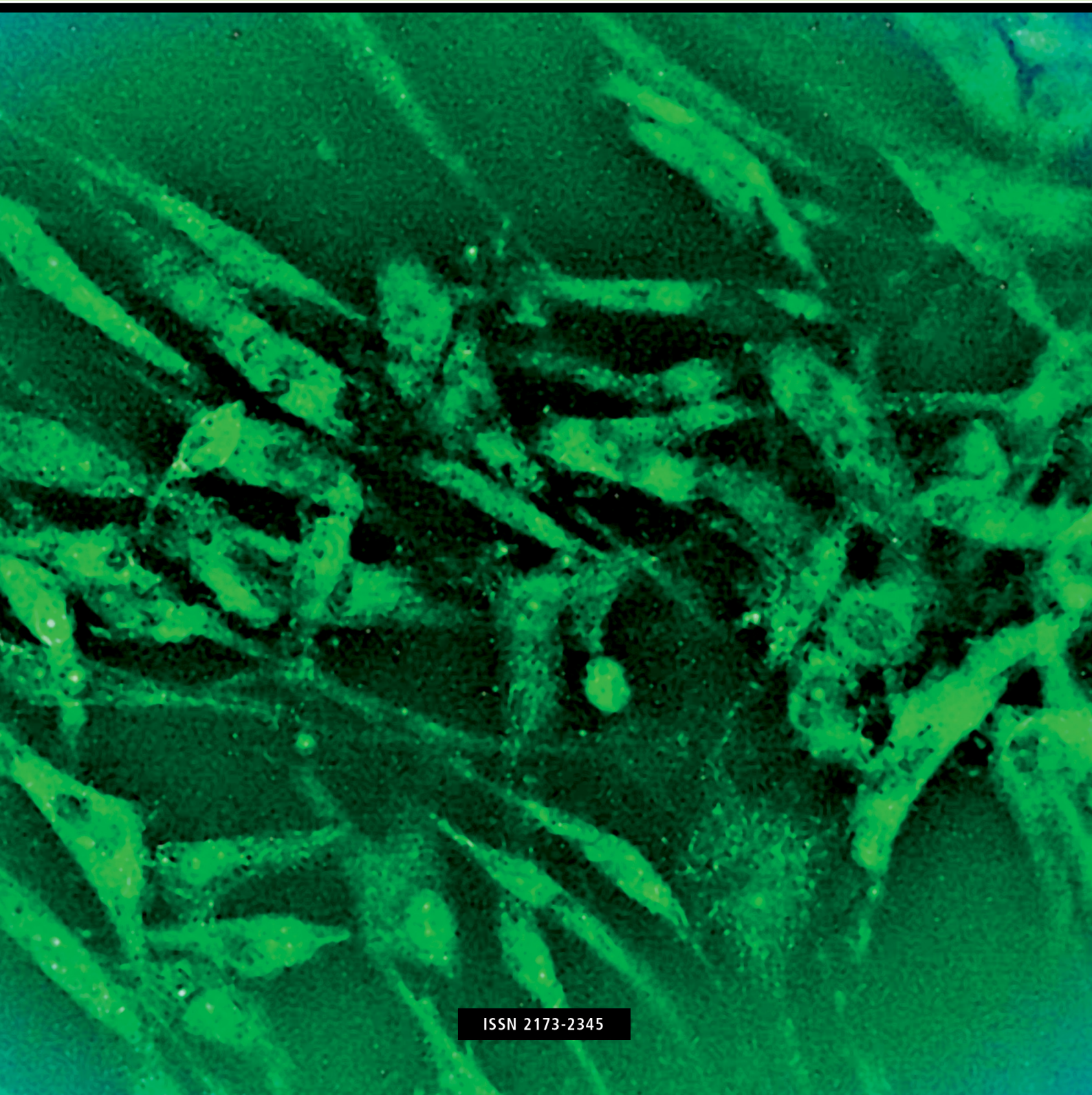

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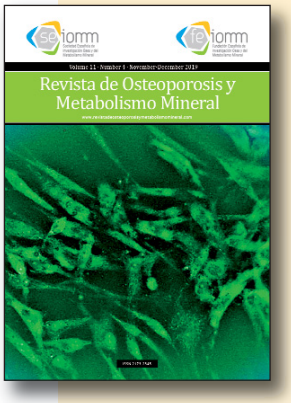

Our cover: Oxidative stress labeling in primary osteoblasts by CellROX Green Reagent (Thermofisher).
Author: Dra. Natalia García-Giralt. Hospital del Mar Medical Research Institute (IMIM). CIBER of Fragility and Healthy Aging (CIBERFES). Barcelona, Spain).

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Summary

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About air pollution and hip fracture

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Raised levels of air pollution have recently been been linked to the induction of inflammatory phenomena at both systemic and tissue levels. Chronic inflammatory diseases, such as rheumatoid arthritis or chronic obstructive pulmonary disease, reduce bone mineral density (BMD), which leads to an increase in the release of immune cells from the bone marrow. Particulate matter is associated with oxidative damage and inflammation, which can accelerate bone loss and increase the risk of fractures in older adults. However, the association between air pollution and osteoporosis is not yet well defined in the literature.

It seems that there are other indirect routes, such as vitamin D and PTH, which may also be altered by contamination and are involved in bone remodeling[1-8]. In the first place, air pollution (microparticles and ozone) presents a physical barrier to ultraviolet B solar radiation, thus contributing to a lower cutaneous production of vitamin D[2,4,5]. Similarly, a study conducted in the United States[9] indicated the relationship between low levels of PTH in blood and elevated levels of microparticles and carbon in the air, causing indirect harmful effects on bone mass.

To appreciate the importance of these findings, we should take into account the complex etiology of osteoporosis and its consequence of fragility fractures in the general population. Osteoporosis is a systemic disease. Approximately one third of women and one tenth of men over 50 have osteoporosis or osteopenia. The statistics allow us to calculate that approximately one in two women and one in three men over 50 will suffer a fragility fracture during their lifetime.

These patients are more apt to suffer a second fracture, in addition to developing chronic pain, greater dependence on basic activities of daily living and a reduction in their quality of life.

However, the available literature offers conflicting results. In their study, Prada et al.[9] argue that osteoporosis and fragility fractures may be related to air pollution, since populations in areas of higher environmental concentrations of particles smaller than 2.5 µm presented a lower BMD with higher hospital admission rates for fractures. Chang et al.[1] obtained similar results in their study in Taiwan, where they discovered that air contaminated with higher concentrations of nitrogen dioxide (NO_2), together with carbon monoxide, increased the risk of osteoporosis and fractures.

Mazzucchelli et al.[10] consider the association of the levels of different air pollutants on the incidence of osteoporotic hip fracture in a region of southern Europe, detecting an association between SO_2 and NO_2 and hospital admissions due to hip fracture. In a second study[11], however, these same authors established that at the time of the year with the most adverse weather conditions, such as winter and autumn, there were more cases of hip fractures. Apparently, this phenomenon is due to the fact that at these stages of the year the environment is impregnated with fog and rainwater, and the ground is wet, slippery or covered with tree leaves, which increases the risk of falls and, therefore, fractures, especially those of the hip.

However, in the article published in this issue of the Journal of Osteoporosis and Mineral Metabolism, Ormeño and Quevedo[12] do not find a statistically significant association between environmental pollution and the incidence rate of hospital discharges due to osteoporotic hip fracture in Chile. To its credit, this analysis assesses more than 8,000 hospital discharges in 2017, and, in addition, considering hip fracture as the main objective. As a weakness, it is a retrospective analysis and does not assess the health habits of the population evaluated.

Given the importance of the problem and the different points of view in the literature, we believe more studies are necessary to establish the true relationship between air pollution and osteoporotic fractures. After all, we belong to an ecosystem and everything that alters it can have harmful effects on the fine balance of life.

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

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Air quality and incidence of osteoporotic hip fracture in Chile

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Summary

Objetive: Recent studies show an association between environmental pollution and the risk of suffering an osteoporotic fracture. This study aimed to determine if there is an association between environmental contamination with fine particulate matter ($PM_{2.5}$) and osteoporotic hip fracture.
Material and method: Retrospective incidence study. The Pearson correlation coefficient (r) was used to assess the correlation between the incidence rate of hospital discharges due to osteoporotic hip fracture in Chile and the annual average concentration of $PM_{2.5}$ in the Chilean Health Services in 2017.
Results: In 2017 there were 8,322 hip fractures in adults 65 years of age or older, with a rate per 100,000 inhabitants of 216 and 567 for men and women, respectively. No association was found between environmental contamination and hip fractures in women. Very weak direct association was found between the incidence rate of osteoporotic hip fracture in men and the annual concentration of $PM_{2.5}$ (r=0.074) by Health Services, being statistically not significant (p>0.05).
Conclusions: No statistically significant association was found between environmental pollution and the incidence rate of hospital discharges due to osteoporotic hip fractures in Chile.

Key words: environmental pollution, particulate matter, osteoporosis, hip.

Introduction

Environmental pollution has been associated with a variety of diseases. Among these conditions, cardiovascular[1] and respiratory[2] have been highlighted in the literature.

Air quality monitoring has preferably been oriented to particulate matter. These particles are mainly found in urban areas and come from thermal power plants, industrial processes, vehicle traffic, residential combustion of wood for heating, coal and industrial incinerators. Particulate matter (PM) is classified according to its diameter, depending on the intensity of its impact: particles of diameter less than 10 µg, known as PM_{10}, and diameters less than 2.5 µg, known as $PM_{2.5}$. The $PM_{2.5}$ particles, having a smaller diameter, penetrate into the pulmonary alveoli and enter directly into the bloodstream. This makes them the most harmful contaminant for health and the ones that generate higher levels of premature mortality in the population, ranking as the fifth mortality risk factor in 2015[3]. Exposure to higher concentrations of $PM_{2.5}$ caused 4.2 million deaths and 103 million lost healthy life years (AVISA) worldwide in 2015, representing 7, 6% of total deaths and 4.2% of AVISA[3]. Worldwide deaths attributable to $PM_{2.5}$ increased from 3.5 million in 1990 to 4.2 million in 2015[3].

Environmental pollution has been associated with a variety of diseases, especially those related to diseases of the skeletal muscle system, particulate matter is associated with oxidative damage and inflammation, which can accelerate bone loss and increase the risk of fractures in older adults Studies in Norway show a higher risk of developing osteoporosis and suffering an osteoporotic fracture in the population exposed to higher concentrations of $PM_{2.5}$[4,5]. Recent studies in the US show that for every 4.18 µg/m^3 increase in $PM_{2.5}$ there is a 4.1% increase in hospital admissions for bone fractures in older adults. Low concentrations of parathyroid hormone in blood are associated with individuals who live in areas of higher $PM_{2.5}$ concentration[6].

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In Chile, $PM_{2.5}$ and other air quality variables are measured daily at air quality monitoring stations. In 2017, of the 31 monitoring stations with population representativeness (representing more than 10 million inhabitants of the 17.5 million inhabitants in Chile), 22 of them (69% of the total) presented concentrations above the value of the annual primary standard for $PM_{2.5}$ (20 $\mu g/m^3$)[7]. That same year, more than 8 million inhabitants of Chile (figures close to 50% of the population) were exposed to average concentrations of $PM_{2.5}$ higher than the norm. In Chile's central zone, where there are more than 7 million inhabitants, the average concentrations of $PM_{2.5}$ reach 29 $\mu g/m^3$. Toward southern Chile, the concentrations increase considerably. The city of Coyhaique, which has about 61 thousand inhabitants, is the most polluted city in Latin America, exposed to the highest average $PM_{2.5}$ concentrations (57 $\mu g/m^3$)[7].

The only study in Latin America that evaluates the association between air pollution and osteoporosis was carried out in Chile, analyzing the association between hospital discharges from 2005 to 2011 and the particulate matter. No statistically significant association was found between air pollution and the average annual incidence of osteoporotic hip fracture in Chile. However, data from some cities were used and not data corresponding to the Chilean Health Services, so a large number of hospital discharges were left out of the study[8].

The aim of this study was to determine if there is an association between air pollution and osteoporotic hip fracture in the Chilean population.

Material and method

A retrospective incidence study was conducted.

The National Health Services System (NHSS) of Chile has 29 territorial Health Services (HS) that encoPMass defined geographical territories.

The Ministry of Health's Department of Health Statistics and Information (DHSI) 2017 records were used, from which the amount of osteoporotic hip fractures was obtained for each Chilean HS. The hip fractures correspond to the S72 code of the ICD-10 (tenth edition of the International Classification of Diseases), and hip fractures corresponding to adults 65 years of age or older were used, as these are attributed to osteoporosis.

From the records of the National Institute of Statistics (NIS), the data of the population of 65 years and over by HS were obtained in 2017. The HS data of the number of inhabitants of 65 years or more were used and the number of hip fractures in adults 65 years of age or older by HS to calculate the incidence of osteoporotic hip fracture in each HS.

Data from the National Air Quality Information System (SINCA) were used to obtain the annual average concentration of $PM_{2.5}$ (in $\mu g/m^3$) in each SS. Because not all health services have $PM_{2.5}$ monitoring stations or do not have validated records for 2017, 8 of the 29 HS of Chile were excluded, which means approximately 3 million of the country's inhabitants (17% of the total Chilean population).

With the statistical package SPSS 21.0, Pearson's correlation coefficient was measured (test used to measure the degree of relationship of two linearly related quantitative variables) to assess the association between the annual incidence of osteoporotic hip fracture by HS and the annual average of concentration of $PM_{2.5}$ per HS in 21 of the 29 Chilean HS (representing approximately 14.5 of the 17.5 million inhabitants of the country, 83% of this). A 95% confidence level was used, so the results with $p<0.05$ are considered significant. When interpreting the level of correlation, a value r=1, a very strong correlation 1>r>0.8, a strong correlation with 0.8>r>0.6, a moderate correlation with 0, is considered a perfect correlation. 6>r>0.4, a weak correlation with r 0.4>r>0.2, a very weak correlation with 0.2>r>0, and a null correlation with r=0.

The study has its limitations. It is retrospective and does not assess the health habits of the population evaluated. However, by including most of the HS in Chile, it uses a large part of the population and by including only the 2017 data, it does not present the bias of including population that changed direction in the evaluated years.

Results

In 2017, 8,322 osteoporotic hip fractures occurred in Chile for an estimated population of 17.5 million, according to the 2017 Census. The national incidence rate of osteoporotic hip fractures was 415.4 per 100,000 adults of 65 or older, being lower for men (215.9 per 100,000 men 65 or older) and higher for women (566.8 per 100,000 women 65 or older). The HS with the highest incidence of osteoporotic hip fractures is the HS of Iquique and Tarapacá, while the HS with the lowest incidence is the Eastern Metropolitan Area (Table 1).

In terms of air quality, this was evaluated with annual concentrations of $PM_{2.5}$ in each HS. The annual primary standard for $PM_{2.5}$ is 20 $\mu g/m^3$. Of the 21 HS evaluated, 12 were exposed to average annual concentrations above the norm. The Aysén HS, with approximately 110,000 inhabitants, is the HS exposed to the highest annual average concentrations of $PM_{2.5}$ (48.3 $\mu g/m^3$); while the Magallanes HS, with approximately 161,000 inhabitants, is the HS with the lowest annual average concentrations of $PM_{2.5}$ (5.4 $\mu g/m^3$) (Figure 1).

Regarding the association between the annual average concentration of $PM_{2.5}$ and annual incidence rate of osteoporotic hip fractures by HS, analyzing in men, women and in both sexes, no association was found between the variables, since the coefficient Pearson's correlation (r) is very weak 0.2>r>0 (Table 2). In the dispersion diagram for the incidence of osteoporotic hip fracture due to HS based on the average annual concentration of $PM_{2.5}$, the low attributable relationship between both variables can be seen, since both the HS with the lowest annual concentration $PM_{2.5}$ (Magallanes HS: 5.4 $\mu g/m^3$) as the HS with the highest concentration of $PM_{2.5}$ (Aisen HS: 48 $\mu g/m^3$) had similar osteoporotic fracture incidence rates, 325 per 100,000 inhabitants aged 65 or over in Magallanes HS compared to 398 of Aysén HS (Figure 2).

Discussion

This is the first study that evaluates the link between air pollution and incidence of osteoporotic hip fracture in the Chilean HS, since it could cover most of the country's population, unlike a previous study in which only environmental pollution was evaluated in the main cities of Chile[8].

In our analysis of more than 8,000 hospital discharges during 2017 due to osteoporotic hip fractures in Chile, we found a very weak direct association between the incidence rate of HS in men with air pollution by fine particulate matter and that did not present statistical significance.

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Table 1. Annual average of concentrations of fine particulate material $PM_{2.5}$ and incidence of hip fractures in adults 65 years of age or older in each Health Service (HS) during 2017

	Annual average of concentrations of ($MP_{2,5}$) in µg/m³	Incidence of fractures per 100,000 inhabitants aged ≥65 years	Incidence of fractures per 100,000 men aged ≥65 years	Incidence of fractures per 100,000 women aged ≥65 years
Chile	26.0	415.4	215.9	566.8
HS Arica and Parinacota	11.9	349.9	182.5	484.7
HS Iquique and Tarapacá	12.7	608.7	306.4	863.7
HS Antofagasta	8.4	374.1	202.6	505.8
HS Atacama	12.0	430.5	224.1	606.5
HS Coquimbo	13.5	559.5	258.0	802.0
HS Valparaíso - San Antonio	14.5	399.4	235.9	520.9
HS Viña Del Mar - Quillota	12.0	375.7	168.3	525.5
HS Metropolitan North	28.1	399.7	220.6	528.0
HS Metropolitan West	27.9	406.7	210.3	556.1
HS Metropolitan Central	27.1	339.5	155.3	462.7
HS Metropolitan East	21.7	201.6	94.3	269.4
HS Metropolitan South East	25.1	348.4	194.9	458.6
HS O'higgins	24.8	371.8	199.7	521.0
HS Maule	22.9	410.7	157.9	483.7
HS Concepción	15.7	373.3	200.7	488.9
HS Araucanía South	34.1	423.3	253.0	557.9
HS Valdivia	33.7	431.6	245.7	580.9
HS Osorno	37.2	368.2	183.7	511.6
HS Reloncaví	29.9	310.6	173.6	425.9
HS Aysén	48.3	398.3	244.1	543.5
HS Magallanes	5.4	325.1	171.0	452.5

Figure 1. Annual average concentrations of fine particulate material ($PM_{2.5}$) in the Health Services of Chile in 2017

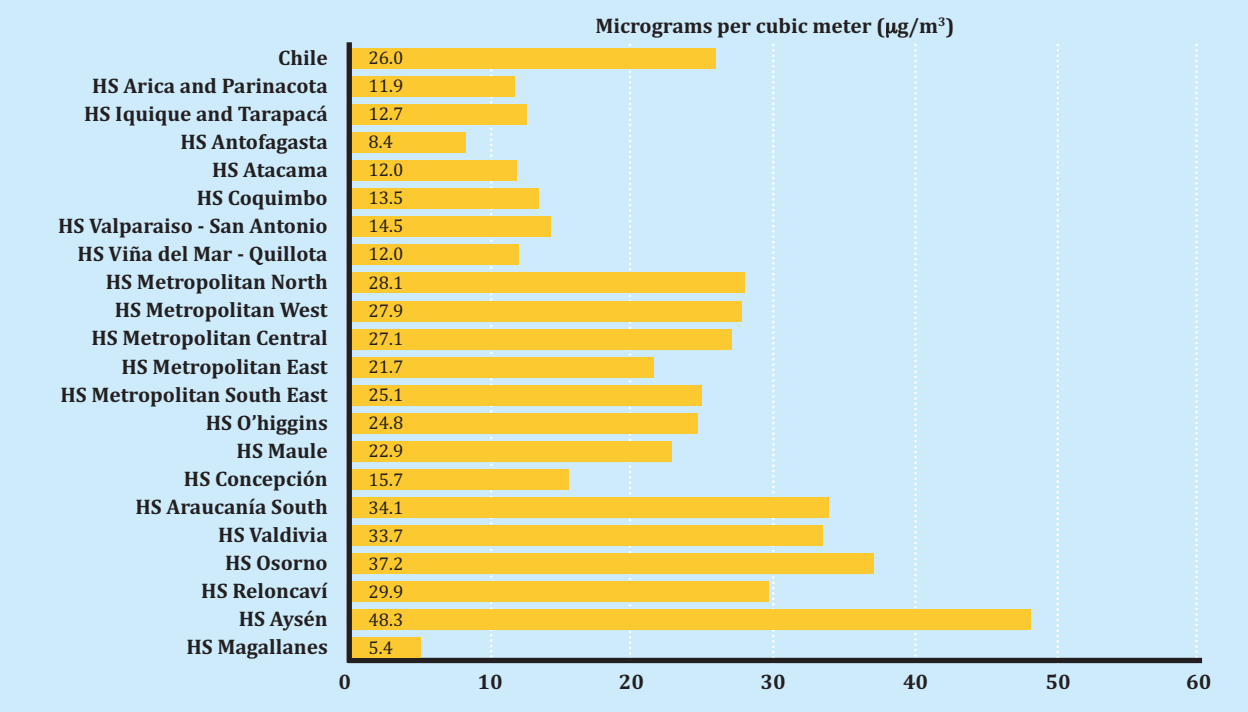
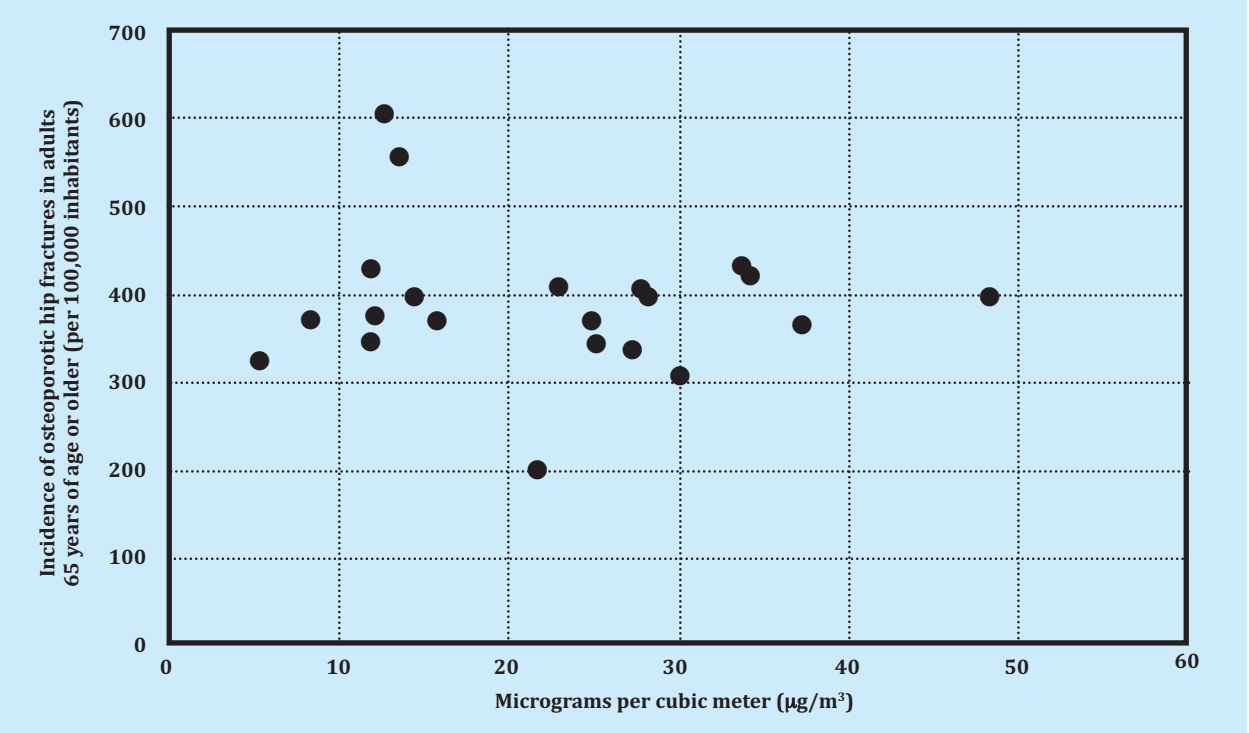


Table 2. Pearson correlation coefficient (r) between the incidence of osteoporotic hip fracture and annual concentration of $PM_{2.5}$ by Health Service, according to gender

	Both genders	Mens	Women
Annual average of concentrations of $MP_{2,5}$	-0.114 (p>0.05)	0.074 (p>0.05)	-0.148 (p>0.05)

Figure 2. Scatter plot of incidence of total osteoporotic hip fractures by Health Service and annual average concentration of $PM_{2.5}$ in each of them



Diddier Prada et al. found an association between prolonged exposure to $PM_{2.5}$ and excessive loss of longitudinal bone. They also found that the population of areas with a higher concentration of $PM_{2.5}$ have a higher risk of suffering an osteoporotic fracture[6].

In 2 studies conducted in Oslo (Norway), a direct and statistically significant association was found between environmental contamination, total bone mineral density (BMD)[4] and forearm fracture[5]. However, given that the part of the population that suffers osteoporotic hip fractures may have a normal BMD or in the range of osteopenia, for our study we decided to evaluate the osteoporotic hip fracture instead of BMD.

A study in Taiwan found lower BMD values at higher concentrations of environmental pollutants[9], with a low relative risk, but which is important given that a large part of the world's population is exposed to polluted air. In this work, the lower BMD was associated with the impact of environmental pollutants at bone level, since bone is a lifetime reserve for heavy metals. Lead and other toxic metals such as cadmium, mercury and aluminum form bonds with the calcium of hydroxyapatite, resulting in a biological waste for life, since more than 90% of the lead in the human body is found in the bones and on the teeth[10].

In conclusion, in our retrospective analysis of more than 8,000 hospital discharges of 2017 due to osteoporotic hip fractures in Chile, we found no association between the incidence rate of HS with air pollution, represented by the annual average concentration of $PM_{2.5}$.

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

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Long-term efficacy and safety of polymethylmethacrylate (PMMA) in osteoporotic patients treated by percutaneous vertebroplasty

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Summary

Objetive: Currently, there are limited data on the long-term influence of polymethylmethacrylate (PMMA) on the integrity of vertebral bodies after percutaneous vertebroplasty (PVP). Interesting investigation is being carried out into the possible relationship between this technique and the appearance over time of osteolytic phenomena or cement fragmentation in the intervened vertebrae. The objective of our study was to investigate whether there is a loss of effectiveness and/or safety of PVP with PMMA in the long term.

Material and methods: X-rays were analyzed of intervened patients corresponding to the immediate post-operative and the most recent radiological study (PVP more than 15 years previous). With both radiological studies, we describe: the height of the vertebral body, the angulation of lamellar plates and osteolytic presence around the cement over time.

Results: A total of 7 patients operated by PVP with PMMA 15 or more years earlier agreed to have a new radiograph in our center. After the analysis of their post-operative images (immediate and 15 or more years after surgery), no loss of height of the cemented vertebral body, differences in angulation in the lamellar plates, presence of osteolysis around the vertebrae was observed in any of the involved vertebrae cement or fragmentation of the injected PMMA.

Conclusion: PMMA injected into the vertebral body remains stable over time (more than 15 years). There are no changes in the bone-PMMA interface, osteolysis and/or changes in the height of the vertebral bodies in the cases analyzed.

Key words: vertebroplasty, PMMA, spine surgery, vertebral fracture, osteoporosis, osteolysis.

Introduction

Without a doubt, vertebral fracture (VF) is the most prevalent type of bone rupture in patients with low bone mass[1]. The most recent epidemiological data in the Spanish population indicate about 35% VF prevalence in women over 45 years of age[2]. In men, the prevalence at 50 years is estimated 5 times lower than that of the female population, although this increases beyond 70 years of age[3].

Osteoporotic VFs (OVF) are conservatively treated, usually including rest, analgesia (in combination with muscle relaxants), orthotics and rehabilitation. This treatment is crucial in the first weeks post-fracture, so that proper follow-up usually resolves OVFs effectively. However, in 10-35% of patients, complications may arise from the fracture itself, such as delayed bone union, increased kyphosis, appearance of neurological disorders or the appearance of pseudo-arthrosis (Kümmell's disease). In these cases, patients frequently do not respond well to conservative treatment, complicating the management of their symptoms. This tends to worsen over time[4].

Regarding these patients' failure to respond to conservative treatment, the appearance in recent decades of minimally invasive techniques, such as vertebroplasty (VP) and percutaneous kyphoplasty, has provided a good therapeutic alternative both for managing symptoms and avoiding serious long-term complications.

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VP consists of injecting polymethylmethacrylate (PMMA) bone cement into the fractured vertebral body, with the immediate objective of curbing the vertebra's collapse, increasing its resistance and alleviating pain[5].

The new cements available for use in cementoplasty require preparation in a highly specific monomer/polymer ratio that prevents alterations in the viscosity of the final mixture. This factor is crucial both for a correct polymerization and for the application of the cement itself, since it is during this phase when the mixture is injected into the affected vertebrae of the patient. Thanks to the improvement of its properties in recent years, the new cement mixtures minimize material leaks from the bodies and reduce the thermal effect on the healthy bone surrounding the fracture. Thus, the PMMA is more effective in repairing the OVF as well as making it more secure[6,7]. Although several studies demonstrate VP's short-term efficacy and safety[8-12], its long-term stability has not yet been fully established.

This paper is the first to evaluate the bone status of fractured osteoporotic vertebrae that were cemented by PVP and that have a follow-up of ≥15 years. Our main objective is to assess the long-term bone integrity of the intervened vertebrae, to thus clarify the safety and efficacy of the technique over time.

Material and methods

Study population

We present a series of 7 clinical cases in which their postsurgical follow-up is analyzed descriptively. This is a single-center study, carried out at the Fundación Jiménez Díaz University Hospital (FJD) in Madrid (Spain) with the approval of the Ethics Committee of the same hospital. Thus, for its realization, the monitoring and compliance with the standard ethical standards set forth in the Helsinki Declaration of 1964 and its subsequent revisions is confirmed (Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996, Edinburgh 2000, Seoul 2008 and Fortaleza 2013)[13].

Our study population was selected through a database belonging to our Spinal Pathology Unit (SPU-FJD), where information and other relevant clinical data of those patients operated by PVP are collected by usual clinical practice. As screening criteria, patients with a diagnosis of OVF and with post-surgical follow-up ≥15 years were selected from this database, which met another set of additional criteria described below.

Inclusion and exclusion criteria

The criteria to be met for inclusion within the study population included: having reached adulthood regardless of gender; bone densitometry values (DXA column) compatible with osteoporosis or osteopenia; diagnosis of OVF, failure of conservative treatment reported in the medical history; intervention by percutaneous VP carried out exclusively by SPU-FJD surgeons; and patients who will be clinically and radiologically monitored at 15 or more years after surgery (PO≥15a).

Similarly, patients were excluded who, even if meeting the above criteria, presented VF any non-osteoporotic or doubtful etiology, had presented infection or any other type of post-operative complication and/or were subsequently intervened by instrumentation (instrumented vertebral arthrodesis).

Study variables and image analysis

Data related to the study variables: sex, age at the time of surgery, weight, height, body mass index (BMI), T-score values, number of OVFs, surgical approach, vertebral cementation level (cervical, thoracic, lumbar), presence of osteolysis foci and presence of fragmented material were extracted from the database belonging to the UPC-FJD. All these variables were documented and stored in electronic format, creating a data file owned by the UPC-FJD. Each set of data was recorded in relation to a random code that was assigned to each patient thus guaranteeing the confidentiality of their data[14].

Radiologists from the Neuroradiology Service (FJD) analyzed the images of each patient corresponding to immediate post-operative (PO) (radiographic paper support) and the PO≥15a (exported using Surgimap® software). This analysis searched for vertebral bone alterations, foci of osteolysis around the material and/or cases of fragmented PMMA. In addition, measurements were made of the heights (anterior, middle and posterior) and angulation of the plates of each of the intervened vertebrae.

Statistical analysis

IBM SPSS Statistics 25.0 was used to calculate the median, minimum, maximum and interquartile ranges (descriptive parameters) of the quantitative variables age and BMI.

Results

After reviewing the SPU-FJD database, we obtained a total of 69 records corresponding to patients operated by PVP in our hospital 15 years or older. From this total of cases, we observed 26 follow-up losses (38% with respect to the total number of records) as we were unable to contact these patients or know their current status. However, we contacted a total of 43 patients or their relatives, which allowed us to know a total of 30 cases of exitus (70%) and 13 cases of patients still alive (30%) (Figure 1). Among the living patients, 7 of them agreed to undergo a new radiography, these images being the most recent radiological studies and corresponding to the follow-up PO≥15a after the VP. Thus, we obtained a series of 7 cases of patients having undergone VP surgery with a radiological follow-up of 15 years or more.

This case series consisted of 6 Caucasian women and 1 male whose median age at the time of surgery was 67 years (min=62; max=87, interquartile range=18). The pre-operative BMI had a median of 26.67 (min=18.36; max=31.96, interquartile range=5.21) (Table 1). All patients in this series presented T-score values compatible with osteoporosis or osteopenia before surgery.

In addition, in all cases the OVF intervened was single level (total number of intervened levels within the case series=7), the conservative treatment prior to surgery having been ineffective (Table 1).

SPU-FJD surgeons of the carried out the corresponding surgical interventions, with a uni-portal approach in 5 cases and bi-portal in 2 cases. The intervened vertebrae were in 4 thoracic cases: T7, T11 and T12 (2 cases of the latter) and in 3 lumbar cases: L3, L4 and L5.

The measurements taken by the FJD team of neuroradiologists allowed us to establish that there were no clinically significant differences in the height of the vertebral bodies (anterior, middle or posterior wall) of the patients comparing the PO and PO≥15a times (Table 2).

Similarly, except for case 5, in which the corresponding measurements could not be made, the remaining cases did not show differences in the angulation of the

intervened vertebrae by comparing their PO and PO values ≥15a (Table 2).

In addition, in no case were fractures and/or height losses in segments adjacent to the original fracture (a single case recorded a new non-adjacent fracture). There was no osteolytic phenomena around the injected PMMA or fragmentation in the images analyzed corresponding to PO≥15a (Table 2, Figure 2).

Discussion

OVFs constitute the most common simple fracture worldwide. In fact, in our country, the Spanish Society of Geriatrics and Gerontology (SEGG) provided data in 2017 that documents a 3-fold higher incidence of this type of fracture compared to hip fractures[15].

Recent research lines have shown that, in addition to osteoporosis, factors such as advanced age, high BMI and/or fractures in thoracic levels (especially in the thoracolumbar junction) are significantly related to the failure of conservative treatment[16,17]. According to the clinical practice carried out in our center, we can establish a failure rate of conservative treatment in the management of acute OVFs of around 15%. These data are similar to those reported by some authors who place it close to 20% according to the specific type of VF[18]. In the series of 7 patients that we presented, all women were operated on in an advanced postmenopausal age, while the male patient underwent surgery was octogenarian. In addition, 3 patients presented BMI values compatible with overweight and 1 with obesity. As for the intervened vertebral level, 4 patients presented fractures in the thoracic vertebrae, of which in 2 cases the T12 (thoracolumbar junction) coincided. These data seem to support the relationship between the aforementioned risk factors and the failure of conservative treatment in their fractures.

Beyond 65 years of age, especially in women, the maximum level of prevalence of OVFs in the Spanish population is reached. Thus, our study accurately represents this situation with the case series analyzed. The profile of the recruited patients would be within a population group that, due to their demographic and physiological characteristics, is at risk of suffering an OVF.

Faced with an OVF with symptoms that cannot be managed by conservative treatment, PVP presents an effective option in the improvement of the patient's pain, functional status and quality of life, even in elderly cases[19-22].

The safety and immediate effects of PVP are well documented in the literature[23-27]. However, so far, there are very few data that continue to demonstrate the effectiveness and safety of this technique in the long term[28,29]. In fact, the post-op follow-up periods published do not generally exceed 2 years[9-12].

According to the latest data from the National Statistics Institute (NSI) updated in 2018, the life expectancy of the Spanish population stands at 83 years, taking into account both sexes[30]. This increase in the aging of the population provides new information that allows us to show PVP as a safe technique in the longer term.

Figure 1. Summary graph of the study population. From a total of 69 patients operated by VP 15 or more years ago in our hospital, a total of 43 patients/relatives (62% of the total) were contacted. After confirming 70% of cases of death, the remaining 30% (13 patients) are invited to go to the hospital for a new radiological study (PO≥15 years). Finally, 7 patients accept and form the case series on which the study is based

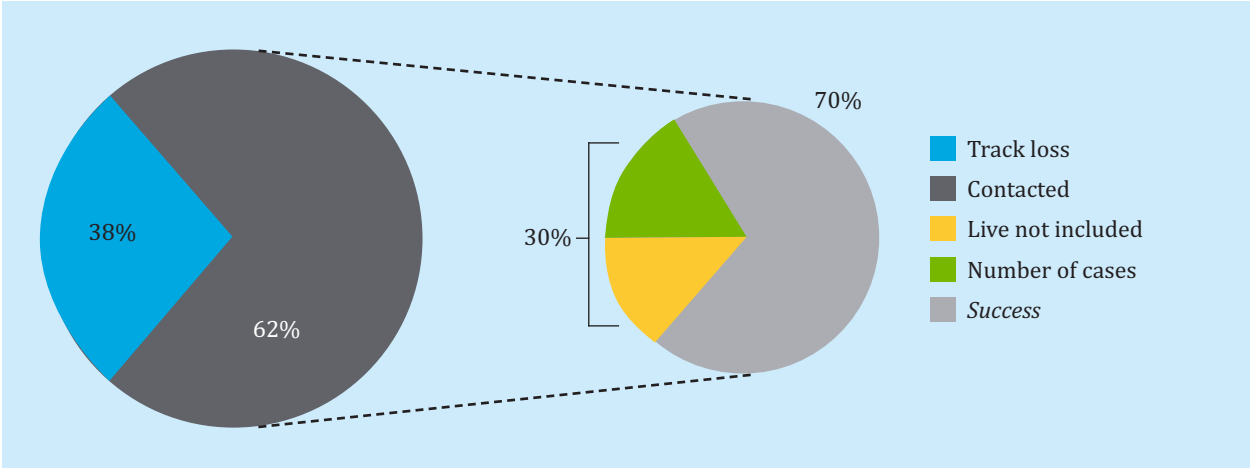

Table 1. Demographic data of the series of 7 patients operated 15 or more years ago by VP in the SPU-FJD

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Age Qx (years)	82	64	65	62	69	67	87
Sex (M/F)	M	F	F	F	F	F	F
Race	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian	Caucasian
BMI	18.36	31.96	22.26	23.61	26.84	27.47	26.67
DXA column (T-score)	-2.3	-2.0	-2.1	-3.2	-2.1	-2.0	-2.8

Age Qx: age at surgery; M: male; F: female; BMI: body mass index; DXA: dual energy x-ray absorptiometry.

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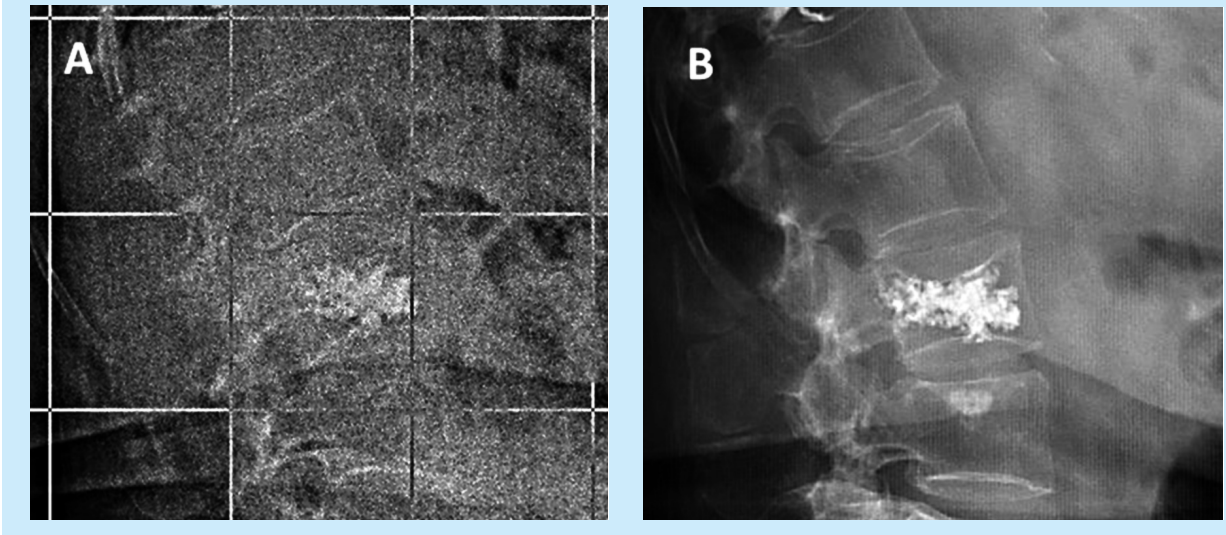
Table 2. PVP characterization, vertebral PO and PO measures ≥15a and data related to the presence of osteolysis/ fragmentation foci of the PMMA of the series of 7 operated patients

	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7	
Cemented level	T11		T12		L5		L4		L3		T7		T12	
Qx approach (U/B)	U		U		U		U		U		B		B	
Vertebral body height (mm)	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**
Anterior wall	10	10.1	28.2	25.3	26	26	27	26.8	21	20.2	20.1	19.7	20	19.9
Middle wall	13	12.8	27.6	25.2	26	26.5	27	26.8	20	19.2	22	22	26	25.8
Back wall	32	31.6	33.1	31.1	31	29.9	30	29.8	27	26.2	29	28.3	33	33.8
Saucer angulations (°)	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**	**PO**	**PO ≥15a**
Local	28	28	6	5	4	4	2	2	-	-	11	11	18	18
Regional	27	27	3	3	18	18	1	1	-	-	24	24	32	32
Bone alterations/PMMA (YES/NO)	**PO ≥15a**		**PO ≥15a**		**PO ≥15a**		**PO ≥15a**		**PO ≥15a**		**PO ≥15a**		**PO ≥15a**	
Fx adjacent segment	NO		NO		NO		NO		NO		NO		NO	
Osteolysis spotlights	NO		NO		NO		NO		NO		NO		NO	
Fragmented PMMA	NO		NO		NO		NO		NO		NO		NO	

T: thoracic vertebra; L: lumbar vertebra; QX approach: surgical approach; U: uniportal; B: biportal; PO: immediate post-operative; PO≥15a: post-operative at 15 or more years of follow-up; Fx: fracture.

Figure 2. Stability and absence of PMMA fragmentation 15 years post-PVP. Radiological images of the immediate PO (A) and PO ≥15a (B) after the VP of one of the patients included in the case series (Case 1)



In addition, there is some controversy among authors regarding a possible relationship between the realization of PVP and the appearance over time of new FV[31-33]. This reason justifies the analysis, such as the one we present here, where post-surgery follow-ups are recorded much longer over time.

In the 7 cases presented, the patients presented stability in the intervened vertebral bodies at the level of the anterior, middle and posterior walls with 15 or more years elapsed from the time of surgery. There are some published data that associate changes in the angulation of the lamellar plate after VF as a risk factor in the appearance of new VF[31,34]. In our series of patients analyzed, there were no clinically significant differences in this angulation after 15 or more years post-op which could justify, together with other factors such as maintenance of osteoporotic treatment, that these patients have not suffered new VF in adjacent segments.

The local response of the host to PMMA has been studied as a long-term phenomenon mainly in cases of implantation of total hip prostheses (THPs). In this type of prosthesis with peri-prosthetic cementation, the development of an inflammatory response by the surrounding bone to the implant cement is common. This reaction

would derive, among other causes, as a consequence of the exothermic process during setting and the release of PMMA particles that appear due to wear and tear due to the compression exerted by the movement itself[35].

Unlike the PMMA of the THPs, in the PVP the cement is interdigitated in the trabecular bone and is not subject to direct compression. This may explain why, as we present in our case series, no PMMA fragmentation or osteolytic phenomena is observed in PO≥15a.

In recent years, new PMMA formulations have been developed, for example, without setting temperature or coated with osteoblasts[36-38]. According to published data, these new cements do not seem to offer much more beneficial effects or greater efficacy than conventional PMMA compared to an OVF. Given current concerns regarding health costs, it would seem illogical to increase this expense in other PMMAs or in more expensive techniques such as balloon kyphoplasty without clinical data that clearly endorse it[39]. In addition, as we present, in our center we observe that 70% of the patients operated 15 or more years ago were exitus due to causes unrelated to their OVF. Meanwhile, those who were still alive presented stability of the injected PMMA after this time.

The present study describes the experience of a small group of patients (n=7 of 13 available) with a similar diagnosis. Due to the limitation in their number of cases there is no way to carry out statistics of inferential type, although descriptive study is possible.

Conclusion

This work constitutes the first evidence of PVP as a safe and effective technique in patients with a follow-up of 15 or more years after their surgery. PMMA kept both heights (anterior, middle and posterior) and vertebral angulation stable, in addition to not causing osteolytic phenomena or observing long-term material fragmentation.

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

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Functional impact of sclerostin gene polymorphisms on DNA methylation and gene expression

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Summary

Introduction: Several genome-wide association studies (GWAS) and others which focused on the sclerostin gene (SOST) have found that some SOST polymorphisms are associated with bone mass and risk of fractures. This study analyzes the functional relevance of certain polymorphisms of the SOST promoter region, and their relationship with the expression and methylation of this gene.

Material and methods: Alleles of the rs851054, rs851056, rs10534024, rs1234612 polymorphisms and DNA methylation were analyzed by pyrosequencing in serum and bone samples of 33 patients undergoing hip replacement. In addition, SOST expression was studied in bone samples. Also, different alleles of the SOST promoter were cloned into double reporter vectors with the luciferase gene under this promoter and the alkaline phosphatase gene under a constitutive promoter.

Results: Methylation analysis of the SOST promoter region in serum free DNA and bone DNA revealed no statistically significant differences across the alleles of the analyzed polymorphisms ($p>0.05$). However, transfections with reporter vectors showed high transcriptional activity, regardless of the vector used.

Conclusion: We have not found a clear association between the different alleles and the DNA methylation of the SOST promoter region. Further studies are needed to determine the polymorphisms' functional effects on the methylation and expression of the SOST gene and the consequences on bone mass.

Key words: serum free DNA, DNA methylation, polymorphisms, sclerostin, osteoporosis, gene regulation.

Introduction

Genome-wide association studies (GWAS) and candidate gene studies have found some single nucleotide polymorphisms (SNPs) in the SOST gene, which encodes sclerostin, associated with bone mineral density (BMD) and predisposition to fractures[1-4]. However, the mechanism responsible for this association is unknown. Among the general mechanisms by which genetic variants predispose to complex diseases are epigenetic mechanisms, such as DNA methylation, that modulate gene transcription directly (locally) or indirectly (remotely)[5]. In this sense, it should be noted that the DNA methylation of the SOST promoter is inversely related to the gene expression levels of the gene[6].

DNA methylation is an epigenetic mark that consists in the addition of a methyl group at the 5 'position of the cytosine ring, usually in cytosines that precede guanine, forming the so-called CpG sites. They are distributed throughout the genome and abundant in some specific regions, such as promoters, called CpG islands. Methylation levels of CpG sites and/or islands have specific profiles according to the tissue of origin and modulate gene expression in many tissues, including bone[7-10].

Circulating cell free DNA (cfDNA) is present in fluids, such as urine, synovial fluid, plasma or serum, and it is an interesting molecular biomarker because it is easy to obtain without using invasive procedures[11]. cfDNA is being extensively studied as a biomarker in the oncology field, for the amount of cfDNA increases with the presence of several tumors. In addition, tumors accumulate specific mutations, which allow them to be differentiated from other DNA sequences with different origin[12,13].

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Therefore, cfDNA is a promising marker for the detection, diagnosis, prognosis, monitoring and treatment of various diseases[14].

Previously, we have demonstrated specific DNA methylation patterns in osteoblast and mesenchymal stem cells (hMSCs) derived from osteoporotic patients. These differentially methylated regions are enriched in genes associated with cell differentiation and skeletal development, in hMSCs[15] and osteoblasts[16], respectively. Specifically, we have previously verified that DNA methylation levels of the SOST promoter regulate gene expression in osteoblasts. Hence, DNA demethylation induces SOST expression, even in cells in which this gene is normally repressed[17,18].

This study aims to determine DNA methylation levels in the SOST promoter from serum free DNA and the possible relationship with some polymorphisms previously associated with BMD. In addition, we considered the effects of these polymorphisms on the expression of sclerostin.

Material and methods

Patient selection

Femoral heads were obtained from 33 patients undergoing hip replacement surgery for osteoporotic fracture (FRX; n=15) or osteoarthritis (OA; n=18). Patients with secondary osteoporosis, secondary osteoarthritis or fractures due to high-energy trauma were excluded. Patients' age ranged between 61 and 91 years. From each patient, samples of bone tissue, blood and serum were obtained. The serum was used to isolate free DNA and study sclerostin promoter methylation. Blood samples were used to obtain genomic DNA in order to analyze the polymorphisms of interest.

The study was approved by the Ethics Committee in Clinical Research of Cantabria and patients gave their written informed consent.

DNA isolation

Trabecular bone samples from the central part of the femoral heads were obtained with a trocar. They were instantly frozen with liquid nitrogen and homogenized with a polytron in lysis buffer and proteinase K. After an overnight incubation at 55°C, DNA was extracted with phenol: chloroform: isoamyl alcohol, as previously published[16]. Cell free serum DNA was extracted from two 1 ml aliquots of serum, proccessed in parallel (2 ml of serum per patient for analysis). To each aliquot, in a 15 ml falcon tube, we added 500 µl of lysis buffer (Tris-HCl, EDTA, sodium acetate and SDS) and 5 µl of proteinase K (20 mg/ml). The mixture was incubated for 1 hour in a water bath at 56°C. DNA was extracted, as with bone, by using phenol: chloroform: isoamyl alcohol. The pellet (not visible) was allowed to dry at room temperature and resuspended with 20 µl of distilled water. Blood cell DNA was extracted with the Illustra blood genomic kit Prep Mini Spin (GE Healthcare Life Sciences, Marlborough, USA.).

Genotyping

Blood cell DNA was quantified by the Qubit procedure (Thermofisher Scientific, Waltham, USA). Four SOST SNPs previously associated with bone mineral density (rs851054, rs851056, rs1234612 and rs10534024) were analyzed by using assays with Taqman probes (Thermofisher).

DNA methylation analysis

500 ng of bone DNA per sample was used to modify with bisulfite with the EZ DNA Methylation-Gold methylation kit (ZymoResearch, Irvine, USA), following the manufacturer's instructions. On the other hand, the whole amount of DNA isolated from serum (20 µl of the resuspended DNA) was used and also subjected to bisulfite modification with the EZ DNA Methylation-Gold kit. The level of CpG methylation in the region of the SOST promoter was analyzed by pyrosequencing (PyromarkQ24 Advanced System®). The primers used for PCR amplification and sequencing were designed with the PyroMark assay designer (Qiagen NV, Hilden, Germany) (Sense primer. 5'-TGGTGGGGTGATAAATGAATT-3'; Antisense primer. 5'-TGGTGGGGTGATAAATGAATT-3'; Sequencing primer 5'-ATTTGGTTTGAGAAATGG-3 '). The PCR was carried out with a biotinylated primer, which allows its purification in a single-stranded DNA template, using the PyromarkQ24 vacuum workstation (Qiagen N.V., Hilden, Germany) (according to the manufacturer's instructions). Finally, pyrosequencing reactions and methylation quantification were carried out in a PyroMark Q24 Advance System (Qiagen N.V., Hilden, Germany).

The region where methylation was studied was located near the polymorphisms examined, approximately 300 base pairs upstream the transcription start site (Figure 1A).

SOST expression and sclerostin levels

Serum sclerostin levels were analyzed by ELISA (Teco Medical Group, Sissach, Switzerland). The sensitivity of this kit is 0.05-3 ng/ml.

SOST expression in bone was analyzed by quantitative real-time PCR (RT-qPCR). RNA was extracted from frozen bone biopsies homogenizing with trizol, isolating with chloroform and precipitating the RNA with isopropanol. Complementary DNA (cDNA) was synthesized with the TaKaRa PrimeScript RT kit (TaKaRa, Shiga, Japan). We used 1 µg of starting RNA, random hexamers and oligo-dT as primers, with the protocol recommended by the manufacturer. The transcript levels were evaluated by RT-qPCR using commercially available Taqman assays (Thermofisher Scientific) in an Applied Biosystems 7300 real-time PCR system. We used GAPDH and TBP as reference genes.

Reporters vectors and analysis of transcriptional activity

The SOST promoter reporter vector (HPRM50859-PG04; GeneCopoeia, Rockville, USA) was acquired. In addition, a second vector was obtained with the same sequence, but varying the haplotype (rs851054 G/A; rs851056 C/G; rs851057 C/G). Both vectors have the luciferase gene under the SOST promoter sequence and the bioluminescent alkaline phosphatase gene under a constitutive promoter (Figure 1B). This dual vector allows to normalize the signal and objectively quantify the signal generated by each transfected promoter. Likewise, we obtained a vector with an empty promoter (pEZX-PG04; GeneCopoeia, Rockville, USA) on the luciferase sequence, as a negative control for transfection.

Transfection of the different vectors was carried out with Lipofectamine 3000 (Thermofisher Scientific, Waltham, USA). For the transfection experiments 50,000 cells (HEK-293T) were seeded per well, in a 24-well plate, by triplicate. The next day, with a confluence of 80%, approximately, 500 ng of each vector was transfected, in independent wells, using Lipofectamine 3000 according to the manufacturer's recommendations. The luciferase and alkaline phosphatase signal was analyzed after 24 h, 48 h and 72 h, by using the Secrete-Pair Dual Luminescence Assay Kit (GeneCopoeia, Rockville, USA).

Analysis of the results

The presence of linkage imbalance and haplotypic distribution was analyzed with the Haploview program[19].

Statistical analyzes for this study were carried out using version 3.6.0 of the R software. Alleles were compared with respect to their level of SOST promoter methylation and/or SOST expression in bone by analysis of variance (ANOVA). The comparison between patient groups was performed using Student's t. In all cases, p values less than 0.05 were considered as significant.

Results

Serum free DNA methylation samples were analyzed, in duplicate, by pyrosequencing. DNA methylation levels were taken as reliable when the signal strength was solid. Variability among serum duplicates was small, with an average standard error of 3.89%.

Serum free DNA methylation analysis did not reveal statistically significant differences in relation to the various alleles of the analyzed polymorphisms (rs851054, rs851056, rs1234612 and rs10534024) (Figure 2). We did not find differences in bone DNA methylation in association with the aforementioned polymorphisms (Figure 3).

In addition RNA was also obtained from bone biopsies in order to study the endogenous expression of SOST in bone. The results obtained by RT-qPCR did not reveal statistically significant differences in the endogenous expression of SOST in bone, in relation to the polymorphisms analyzed (Figure 4).

It should be noted that 3 of the 4 SNPs were in strong linkage imbalance, with D 'of 1 and close correlation between their alleles (R^2 of 0.83-1). The other polymorphism, rs1234612, was not part of that block (Figure 5). Combined haplotype or genotype analysis did not reveal statistically significant associations with methylation or gene expression (data not shown). Transfections with reporter vectors, which carried the promoter sequence of the SOST gene, showed high transcriptional activity, regardless of the alleles present in the vector. In fact, it increased up to 20 times at 24 hours with respect to the empty vector. However, both constructions, with opposite alleles, showed a similar activity (Figure 6).

Discussion

Sclerostin is a potent inhibitor of the Wnt pathway. It blocks the co-receptors Lrp4, 5 and 6, thus preventing the receptor activation by Wnt ligands. Sclerostin has an important role in bone biology. Mice with SOST gene deletion have ibcreased bone formation and bone mass[20]. In contrast, overexpression of SOST in osteoblasts decreases bone mass[21]. In addition, certain SOST gene mutations that cause a loss of sclerostin in humans are associated with high bone formation activity and high BMD, causing Van Buchem disease or sclerosteosis[22,23]. Conversely, a monoclonal antibody that blocks sclerostin (romosozumab) has recently been approved by the FDA (US Food and Drug Administration) for osteoporosis treatment, after observing that it increased bone mass in animal studies and in humans[24,25].

Figure 1. (A) Diagram of the promoter region of the SOST gene and location of the analyzed polymorphisms, with the distance to the transcription start point (TSS). The CpG dinucleotide chosen to determine the methylation levels of is also shown. (B) Reporter vectors with the luciferase gene (G-LUC) under SOST promoter and alkaline phosphatase (SEAP) under the constitutive cytomegalovirus (CMV) promoter. Two vectors were used, with a different haplotype of the frequent polymorphisms of the region (rs851054, rs851056 and rs851057)

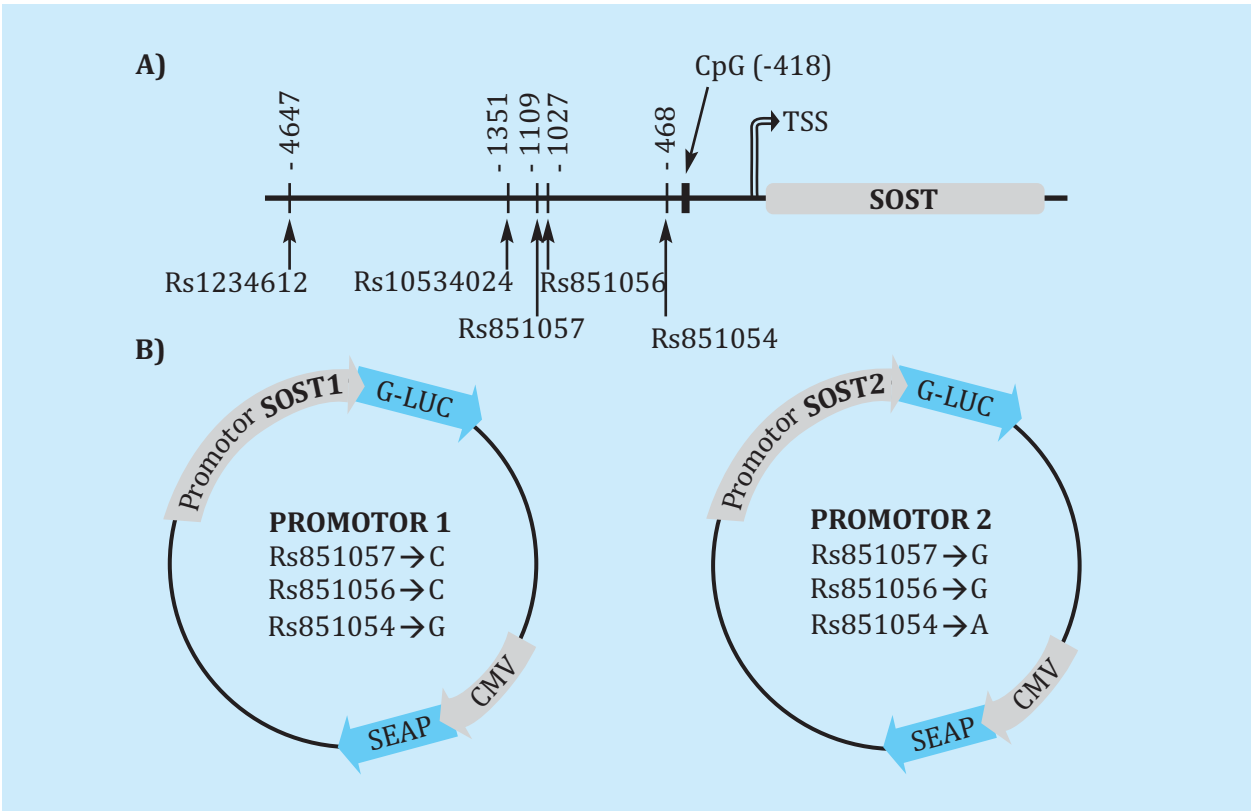


Figure 2. Methylation level of the SOST promoter in serum cell-free DNA ofindividuals (n=33) genotyped for each of the 4 polymorphisms (rs851054, rs851056, rs10534024 and rs1234612). P-values of the analysis of the variance of methylation levels across genotypes

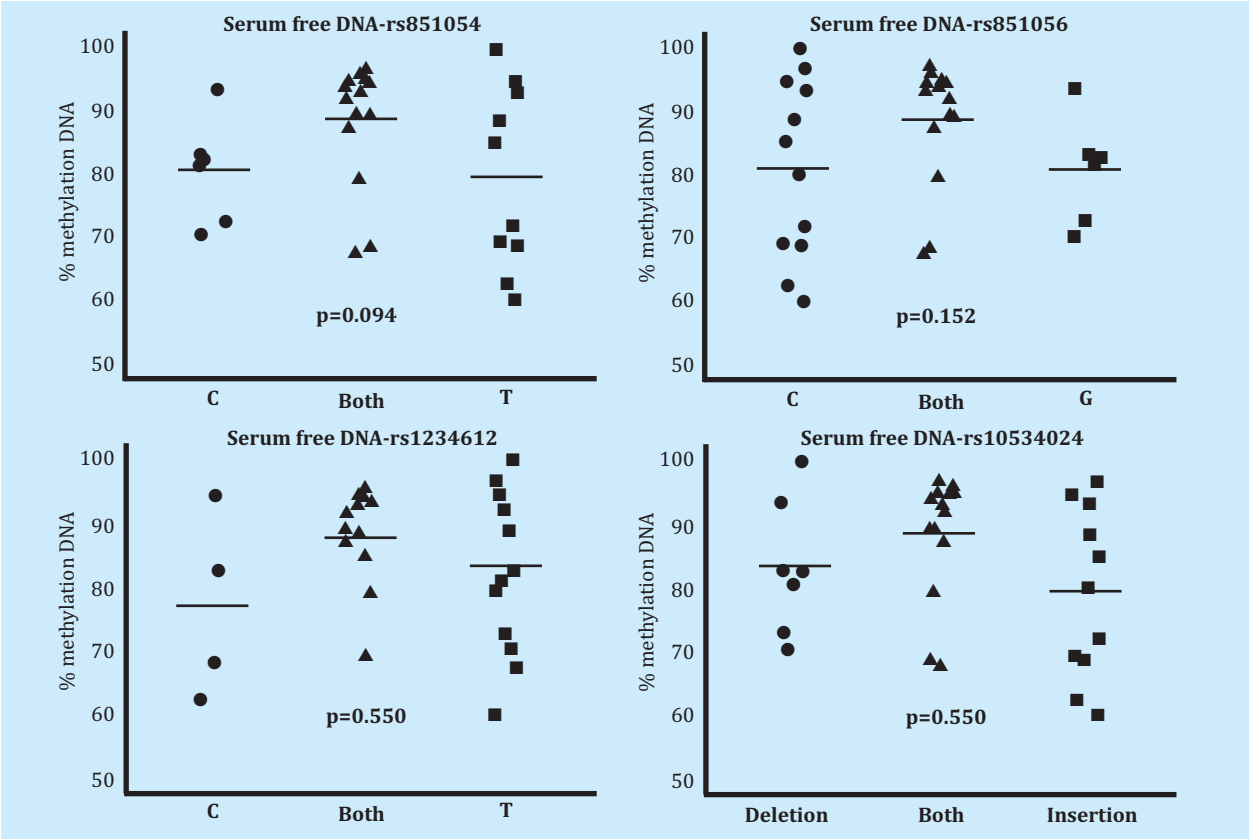


Figure 3. Methylation level of the SOST promoter in bone DNA of individuals (n=33) genotyped for each of the 4 polymorphisms (rs851054, rs851056, rs10534024 and rs1234612). P-values of the analysis of the variance of methylation levels across genotypes

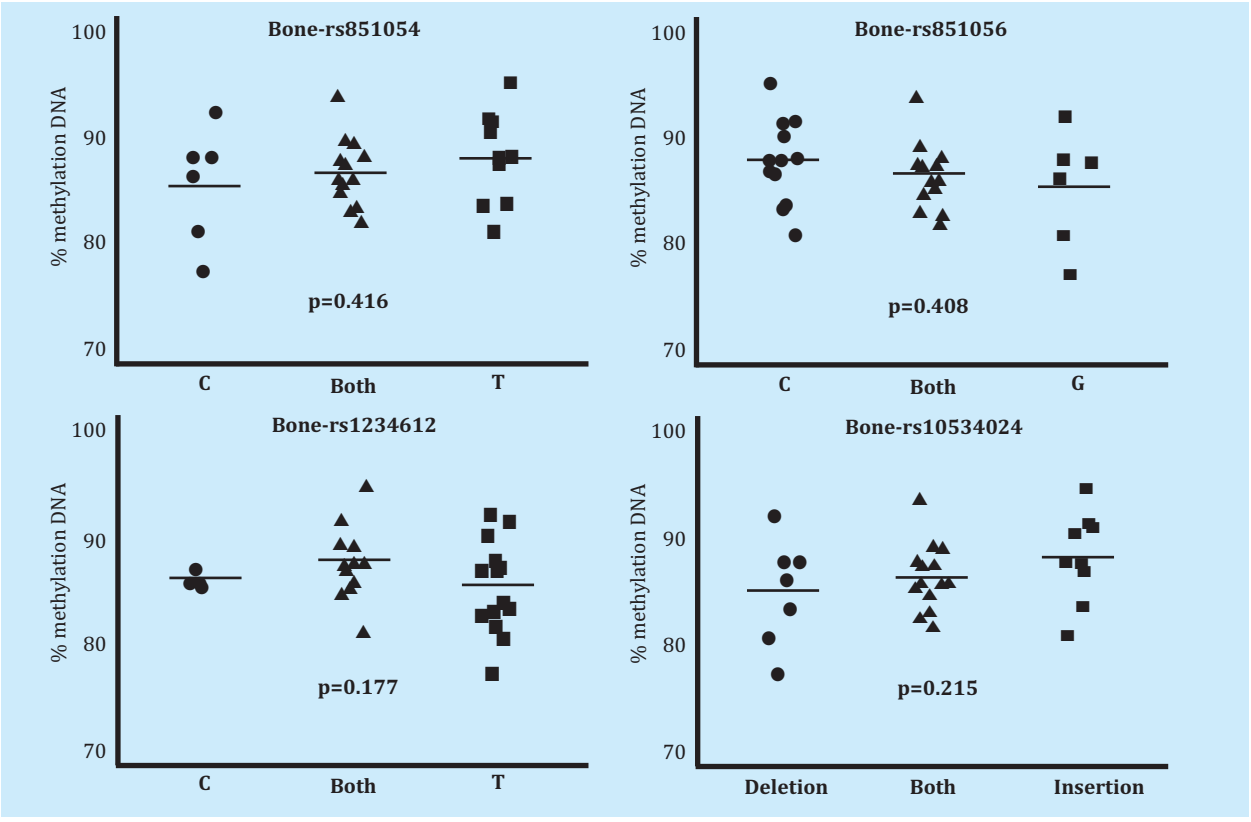


Figure 4. SOST expression in bone. Samples of individuals (n=33) genotyped for each of the 4 polymorphisms (rs851054, rs851056, rs10534024 and rs1234612). Expression levels were calculated by RT-qPCR, standardized by the reference genes (GAPDH and TBP) and are expressed as deltaCt. P-values of the analysis of the variance of methylation levels across genotypes

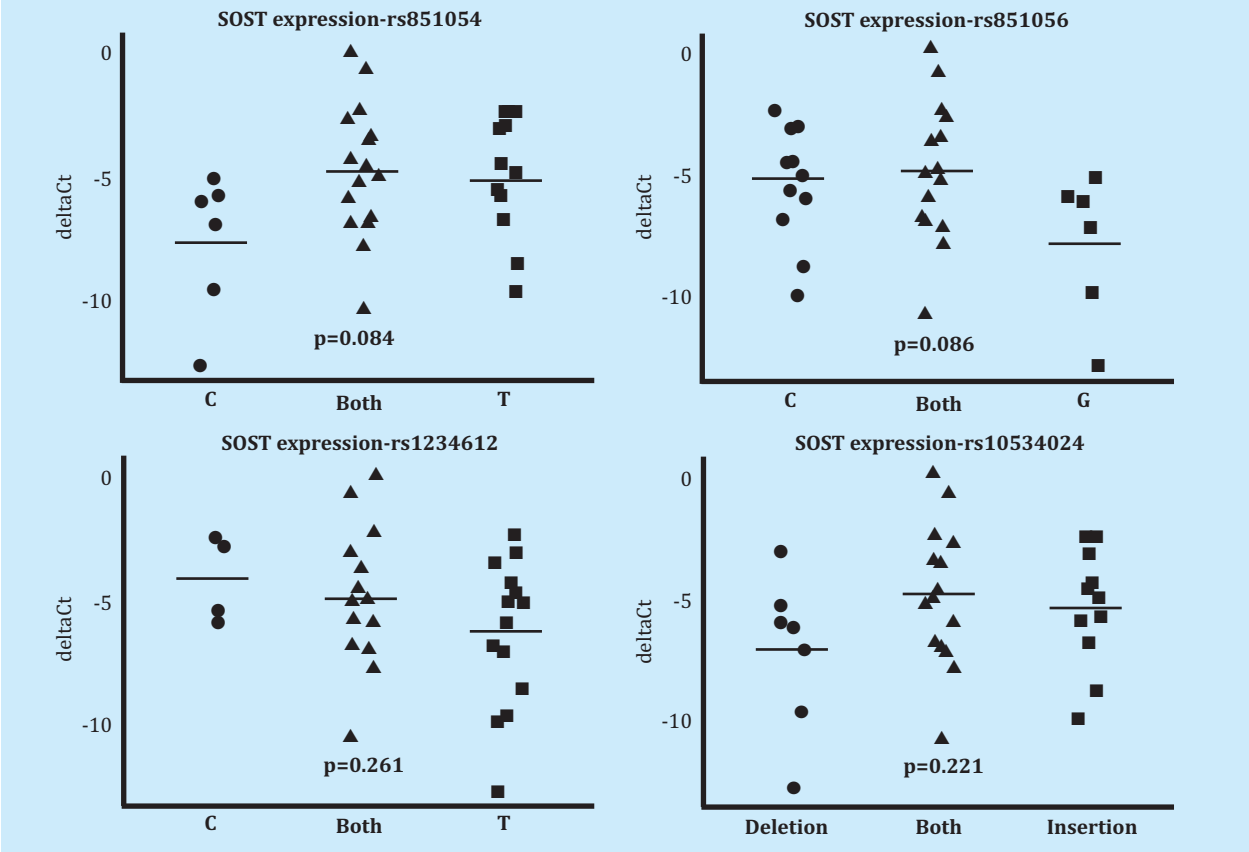
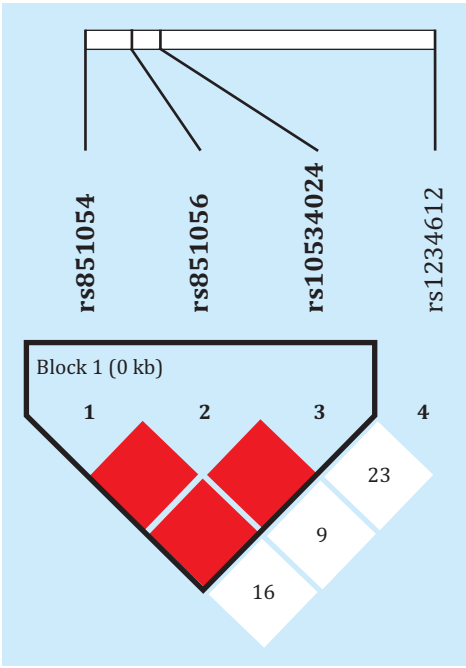


Figure 5. Linkage disequilibrium between the polymorphisms analyzed. The numbers represent the distance values D', which can range from 0 to 1. The figure represents the values multiplied by 100. In the case of color boxes, the value is 1



Several studies suggest that some allelic variants of the SOST gene may influence BMD and the risk of osteoporosis[26,27]. Since these are non-coding variants, presumably they influence the expression of SOST gene. On the other hand, we have previously been able to demonstrate the importance of DNA methylation in the regulation of sclerostin expression in the osteoblastic lineage[18]. Likewise, in several studies it has been shown that genetic variants can influence DNA methylation and SOST gene expression[5]. Hence, the objective of this study was to explore the functional impact of some frequent polymorphisms in the promoter region of the SOST gene, specifically, their effect on methylation and gene expression. However, despite its association with BMD[15], we have not found any significant association between these allelic variants and DNA methylation levels, nor between allelic variants and gene expression levels, whether the analysis was performed at the single SNP level, or at the combined genotype or haplotype levels. In line with this, transfection experiments with reporter vectors have not revealed differences between allelic variants of the promoter region and transcriptional activity. Therefore, our study does not support the existence of an influence of these polymorphisms on the expression of the sclerostin gene, neither direct nor mediated through changes in promoter methylation.

There are several limitations that must be considered when interpreting these negative results. First, the study of association between allelic variables and DNA methylation is limited to a specific region of the promoter. A study of other CpG sites along the SOST region would be needed to obtain a more comprehensive understanding of the potential influence of DNA polymorphisms on DNA methylation. Second, the effect of the polymorphisms studied may depend on other polymorphisms in linkage disequilibrium. In addition, those polymorphisms may be in regions far from the promoter, such as regulatory regions (enhancer) or even in other chromosomes. This fact also limits

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the analysis with reporter vectors, in which only the promoter region of SOST is found. Finally, reporter vectors are transfected *in vitro*, and their DNA sequences are demethylated, so that the *in vivo* situation is not properly recapitulated. Another limitation of this study is the presence of samples obtained from patients with different diseases (osteoporotic fractures and osteoarthritis), that may influence methylation levels distinctly. However, similar results were obtained in the stratified analysis. Finally, the sample size determines the ability to demonstrate subtle differences between polymorphisms, especially in the analysis of combined polymorphisms. In any case, it is important to note that these results do not question the importance of sclerostin in regulating bone cell activity, which has been demonstrated in numerous experimental and clinical studies.

In conclusion, we have not seen a clear association between the different alleles and the DNA methylation of the promoter region of the SOST gene. Therefore, the association of these polymorphisms with BMD does not appear to be due to direct influences on the promoter activity, or to changes in promoter methylation. It can be assumed, therefore, that it is mediated by complex interactions that take place with distant regions of the chromatin. On the other hand, this study raises the possibility of using serum free DNA as a biomarker in some skeletal disorders.

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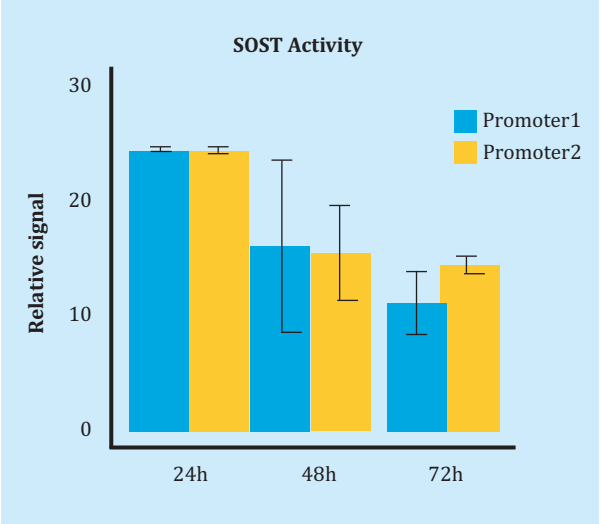
Figure 6. SOST promoter activity measurement by transfecting vectors with different SOST sequences (promoter 1 and promoter 2). Each reporter has the opposite haplotype for polymorphisms rs851054, rs851056 and rs851057. The relative signal was calculated as the ratio of luciferase activity and the alkaline phosphatase activity ratio (SEAP). Subsequently it was compared with the ratio observed after transfecting an empty vector (this is, without the SOST promoter, but with SEAP activity). Bars show the standard error



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

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Factors that influence the results of bone ultra-microindentation tests. An experimental study in rats

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Summary

Objetive: The properties of the materials that constitute the bone tissue are decisive in its mechanical strength but the factors that influence it are partially unknown at present.

Material and methods: In this paper, we gauge bone hardness by means of ultra-microindentation tests with a Berkovich tip and a 150 mN load in femurs of Sprague-Dawley rats subjected to a transverse fracture or a subtraction osteotomy. The results are compared in different bone locations and experimental groups. The study includes the following four experimental groups, each consisting of four rats: a) standard diaphyseal fracture; b) fracture plus osteotomy of 2 mm; c) osteotomy treated with human parathyroid hormone, PTH (1-84); d) osteotomy treated with strontium ranelate.

Results: We found the hardness of the material was consistently greater in cortical bone than in trabecular bone. It was also consistently higher in the upper femoral epiphyses than in the lower epiphyses (difference of 1.2 standard deviations). The surgery reduced hardness in the operated femur (difference of 0.3 standard deviations, $p=5.5 \times 10^{-2}$). PTH treatment induced a slight but consistent increase in hardness at all sites ($p=1.8 \times 10^{-5}$) while the effect of strontium ranelate was inconsistent.

Conclusions: These data show that tissue micro-hardness is influenced by a variety of factors, including anatomy, type of bone tissue, skeletal injury and drug therapy. Therefore, future studies on tissue quality should be carefully designed with these factors in mind.

Key words: bone quality, ultra-microindentation, bone hardness.

Introduction

Fragility fractures are the relevant hallmark of osteoporosis[1]. The risk of fracture is closely related to bone strength, which, in turn, depends on bone mass, geometry and material quality[2-6]. Bone mass and geometry can be evaluated clinically using bone densitometry and high resolution imaging techniques. However, the mechanical properties of bone tissue are more difficult to explore. These properties determine bone quality, a concept that represents the intrinsic capacity of tissue to resist tension states, regardless of the amount of material (bone density) or its spatial distribution (bone architecture). Bone quality depends on the chemical composition and organization of the bone matrix[7].

In an indentation or hardness test, a sample is subjected to quasi-static loading by means of a small indenter, recording the size of the resulting footprint; Sometimes the curve that relates the applied load and the displacement experienced by the indenter during the test is also determined. Hardness is defined as the maximum force applied divided by the area of the footprint that remains in the material after the test. Hardness is the property of the material that characterizes its resistance to permanent/plastic deformation[8].

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Ultra-microindentation (UMI) allows hardness tests to be carried out on the trabecular scale, on individual trabeculae and bone osteons. Several pre-clinical models suggest that the results may be a marker of skeletal resistance. The main advantages of UMI tests are the simplicity of the technique and the ability to map microhardness in different areas of a sample[8]. However, the factors that influence bone tissue hardness results are only partially known, which limits the possibility of carrying out comparisons between studies. This is a relevant aspect, particularly in view of the recent introduction of the ultra-microindentation technique in humans[9]. In this sense, the objective of this study was to explore the variability of hardness in different skeletal locations, as well as the changes induced by various interventions in an experimental model.

Material and methods

Study group. Sprague-Dawley rats (13 weeks old) had been employed as part of a study of delayed consolidation of femoral fractures, using a retrograde intramedullary screw inserted through the intercondylar region of the knee for fixation. Details have been published previously[10]. Study groups (4 rats each) included: a) transverse diaphyseal fracture; b) fracture plus 2 mm diaphyseal subtraction osteotomy (SO); c) SO treated with human parathyroid hormone, PTH (1-84) (30 mcg/kg/day subcutaneously); d) SO treated with strontium ranelate (SR) (900 mg/kg/day orally). Twelve weeks after surgery, the animals were sacrificed, both femurs were removed and stored at -18°C until analyzed.

Hardness tests. The upper and lower epiphyses of the non-operated femurs, as well as the upper epiphysis of the operated femurs, were carefully sectioned and embedded in acrylic resin. The lower epiphyses of the operated femurs could not be analyzed due to alterations induced by screw insertion. The cross sections were polished with silicon carbide paper and subsequently with aluminum oxide with a particle size decreasing to 0.05 mm. Before the test, the samples were immersed in a calcium phosphate buffer solution at 37°C, to mimic the physiological conditions. Hardness was analyzed at 12-15 points randomly selected from the cortical and trabecular regions, using a DUH 211 ultra microindenter test (Shimadzu) with a diamond-made Berkovich tip. The test parameters were as follows: loading speed, 2,665 mN/s; maximum load (P_{max}), 150 mN; load maintenance time, 10 s; download speed, 2,665 mN/s. After discharge, the residual footprint area (Ar) was measured with an optical microscope and the hardness of the material was estimated as P_{max}/Ar.

Data analysis. The study data were distributed in groups according to the independent variables (trabecular or cortical tissue, upper or lower epiphysis, operated or non-operated femur, type of surgery and drug therapy). The UMI data of each group were subjected to a goodness test of fit X^2 to confirm that they were homogeneous and that they followed a normal distribution. Only groups with p>0.95 were considered usable for the purposes of the present analysis. An unpaired two-tailed t-test was used for pairwise comparisons and a p-value with Bonferroni correction was calculated. Next, the overall difference between sets of samples that were similar was estimated except for a single distinctive predictor variable to assess their influence. For this, the Hedge g was calculated, which is equivalent to the difference between groups expressed in Z-score. Random effects models were used for these calculations, implemented in the Meta-Essentials program (www.erim.eur.nl/research-facilities/meta-essentials).

Results

Table 1 summarizes the conditions and the results obtained (the mean and standard deviation of hardness) for each of the 32 experimental groups. The last column ('Analyzable') indicates the result of the goodness test of adjustment X^2; it should be taken into account that only four groups were not analyzed. The g values of the comparisons between groups are represented in figure 1.

As for regional variability, the hardness of the material was consistently greater in cortical bone than in trabecular bone, with an average difference of approximately 0.6 standard deviations ($p=8.0x10^{-4}$, figure 1A). Similarly, the hardness was consistently greater in the upper femoral epiphyses than in the lower epiphyses (standard difference 1.2 units, $p=5x10^{-5}$, figure 1C).

The possible impact of the surgical intervention at the regional level was explored by comparing the hardness in the operated and non-operated femurs. As shown in figure 1B, there was a non-significant trend for the decrease in hardness in the operated femur (difference of 0.3 standard deviations, $p=5.5x10^{-2}$). The standard fracture could only be compared with SO in three groups. This last procedure tended to be associated with a lower hardness ($p=3.7x10^{-2}$, figure 1D).

The effect of PTH was explored in five pairs of groups. The drug induced a slight but consistent increase in hardness at all sites ($p=1.8x10^{-5}$, figure 1E). However, the effect of SR was inconsistent ($p=3.0x\text{-}10^{-1}$, figure 1F).

Discussion

From a clinical perspective, bone mass evaluated by DXA is the most widely used predictor of bone's ability to withstand the repetitive burdens of daily life and other occasional impacts. However, from a mechanical point of view, bone architecture (the distribution of bone mass) and quality (that is, the intrinsic material properties of tissue), are the relevant determinants of global bone strength.

Advanced imaging techniques, such as high resolution computerized tomography (CT) and nuclear magnetic resonance imaging (MRI), can provide useful information about bone geometry, cortical porosity and trabecular microarchitecture. However, bone quality remains a somewhat elusive concept, because biochemical and cellular determinants are incompletely known and not easy to measure. Bone hardness (expressing resistance to plastic deformation) is often used as a marker of tissue quality. In this sense, the determination of hardness is emerging as a technique that provides useful information in clinical studies[11]. UMI tests allow us to obtain other parameters of interest, in addition to hardness, to characterize the mechanical behavior of bone tissue, in particular Young's elastic modulus of the material. However, the available evidence shows that the definition of the test parameters can play a relevant role in the results obtained. In the work of Zhang *et al.*[12] the values obtained for hardness and Young's modulus in bones are compared from nanoindentation and microindentation tests. According to these authors, while hardness is a stable parameter against load values, Young's module is significantly reduced by increasing the load value. For this reason, hardness is preferable when carrying out comparisons with other studies.

Table 1. Experimental groups and hardness values

Group	Tissue	Epiphysis	Intervention	Operated	Drug	N_{tests}	H_{mean} (kp/mm²)	SD (kp/m)	Analyzable
1	Cortical	Sup.	Fracture	Yes	No	52	64.0	12.7	No
2	Cortical	Sup.	SO	Yes	No	48	58.2	6.4	Yes
3	Cortical	Sup.	SO	Yes	PTH	50	62.0	8.1	Yes
4	Cortical	Sup.	SO	Yes	SR	57	67.9	8.9	No
5	Cortical	Sup.	Fracture	No	No	54	60.9	10.0	No
6	Cortical	Sup.	SO	No	No	48	63.1	11.7	Yes
7	Cortical	Sup.	SO	No	PTH	54	65.3	7.2	Yes
8	Cortical	Sup.	SO	No	SR	56	58.5	9.1	Yes
13	Cortical	Inf.	Fracture	No	No	53	52.0	6.9	Yes
14	Cortical	Inf.	SO	No	No	50	49.1	6.2	Yes
15	Cortical	Inf.	SO	No	PTH	49	50.4	5.4	Yes
16	Cortical	Inf.	SO	No	SR	58	53.3	5.6	Yes
17	Trabecular	Sup.	Fracture	Yes	No	53	57.5	7.7	Yes
18	Trabecular	Sup.	SO	Yes	No	53	52.5	6.4	Yes
19	Trabecular	Sup.	SO	Yes	PTH	53	53.3	5.4	Yes
20	Trabecular	Sup.	SO	Yes	SR	57	57.3	5.9	Yes
21	Trabecular	Sup.	Fracture	No	No	51	56.3	5.0	Yes
22	Trabecular	Sup.	SO	No	No	54	56.0	6.6	Yes
23	Trabecular	Sup.	SO	No	PTH	57	57.7	6.0	Yes
24	Trabecular	Inf.	SO	No	SR	57	56.3	5,6	Yes
29	Trabecular	Inf.	Fracture	No	No	51	50.3	7.4	Yes
30	Trabecular	Inf.	SO	No	No	53	52.1	6.4	No
31	Trabecular	Inf.	SO	No	PTH	50	48.7	5.6	Yes
32	Trabecular	Inf.	SO	No	SR	55	54.3	7.1	Yes

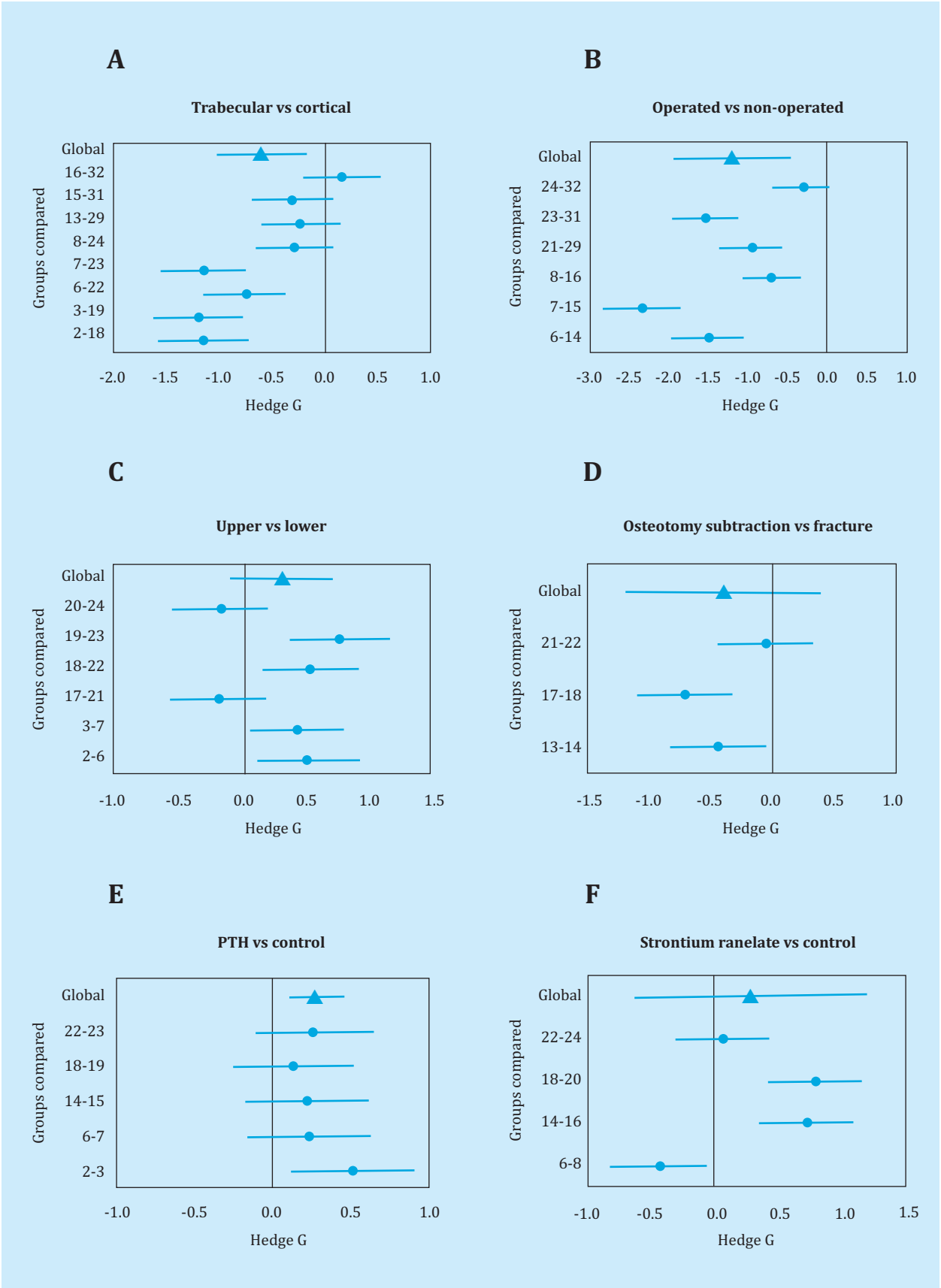
H_{mean}: average; SD: standard deviation; Sup: superior; Inf: inferior; SR: stroncio ranelate.

Due to practical and ethical issues, hardness is usually determined at a single bone point. However, there is little information about the differences in hardness evaluated in different skeletal regions and about the influence of diseases and pharmacological therapies. Therefore, we take advantage of a rat fracture study to try to provide additional information in this important field of research. Our data clearly shows that the hardness is consistently greater in cortical bone than in trabecular bone. Similarly, it is different through individual bones, and specifically, it is greater in the superior femoral epiphyses than in the inferior ones. On the other hand, induced fracture tends to decrease hardness in fractured bone, while PTH increases hardness in all regions analyzed.

Since the determinants of bone hardness have not been fully clarified, the mechanisms underlying these differences remain unknown. However, it is not risky to speculate that they must be related to the matrix composition and, specifically, to its main organic and inorganic components, namely collagen and hydroxyapatite. In fact, the suggested determinants of the mechanical behavior of bone tissue include: collagen orientation, collagen cross-linking profile, degree of mineralization or mineral-matrix ratio, bound water and mineral structure (including the size of the hydroxyapatite crystals)[13]. The orientation of the collagen fiber may be one of the factors responsible for the differences observed between the hardness of the trabecular bone and the cortical bone. Also, different remodeling rates can play a role. Thus, the increase in tissue age is associated with greater microhardness, perhaps due to greater mineralization[14]. Similarly, changes in bone remodeling induced by an injury can help explain the differences we find between the operated and the non-operated femur. The mechanical load has a known anabolic effect on the bone. Therefore, increased load is usually associated with increased bone mass, while discharge causes a rapid loss of bone density. It is less known that mechanical stimulation can cause changes in bone quality[7]. Although the real relevance of such an effect is still unclear, it can also help explain the differences we have observed between skeletal regions and between groups undergoing various interventions. In particular, the lower support of the intervened limb, and consequently the submission to a lower mechanical load, can help explain the lower hardness observed in fractured femurs.

Intermittent administration of PTH or related molecules that activate the PTH receptor, such as teriparatide or abaloparatide, decreases the risk of fracture. The effect of PTH on tissue hardness is controversial. Brennan *et al.*[15] and Amugongo *et al.*[16] reported absence of changes in microhardness in ovariectomized rats treated with teriparatide. On the other hand, Mellibovsky *et al.* indicated that teriparatide improved the properties of the material in patients with glucocorticoid-induced osteoporosis[11]. In this study we found a small but significant effect of PTH on tissue hardness, probably related to PTH-induced changes in bone remodeling[17,18].

Figure 1. Summary of the results obtained in the UMI tests. Hedge g values of the different comparisons between groups. The average value (similar to the standardized mean difference) and the 95% confidence interval of each comparison (circles) are shown. The global value and its confidence interval (triangles) are also included. The numbers on the left axis identify the groups compared, as designated in table 1



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It is interesting to note that, although proteins other than collagen represent only a small fraction of the bone matrix, around 10%, they seem important in determining bone hardness and strength. On the one hand, they contribute to regulate mineralization. On the other, they create bonds with collagen fibers that help absorb and dissipate energy at the nano-structural level[19]. Certainly, some treatments may induce changes in the expression of the genes encoding these proteins, as well as in the amount and spatial distribution of hydroxyapatite crystals, thus constituting another mechanism by which to influence the mechanical properties of the bone matrix.

In summary, although tissue composition and microstructure are probably important factors of tissue resistance, material properties also contribute to bone strength. Our study shows that tissue microhardness is influenced by a variety of factors, including anatomy, type of bone tissue, skeletal injury and drug therapy. Therefore, future studies on tissue quality should be carefully designed with these factors in mind.

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Ethical statement: This work was carried out in accordance with the guidelines of the University of Cantabria and in accordance with EU Directive 2010/63/EU http://eur-lex.europa.eu/legal-content/EN/TXT/?Uri=CELEX:32010L0063.

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How to merge Orthogeriatrics Units with Fracture Coordination Units (FCU). Experience in the Joan XXIII Health Complex of Tarragona

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To the Editor:

Current scientific evidence and practical clinical guidelines recommend primary and secondary prevention of fragility fractures in geriatric patients[1,2]. A personal history of fragility fractures significantly increases the risk of new fractures. Up to 33% of patients with a femur fracture had suffered a previous fracture. Among the various fractures due to fragility, the femur is the most prevalent and presents the most repercussions (clinical, functional and social) in patients over 65 years of age, with the resulting depletion of health resources[3]. The worldwide trend is estimated to rise from 1.7 million femoral fractures in 1990 to 6 million in 2050[4].

In 2011, the Fractures Working Group of the Scientific Advisory Committee of the International Osteoporosis Foundation stressed the importance of coordination between orthopedics, osteoporosis services, fall units, patient, family, geriatrician and Primary Care physician. This multidisciplinary action was consolidated in the so-called "coordinated services for the treatment of fractures" or Fracture Liaison Services (FLS) that were initially implemented in the United Kingdom, Europe, Australia, Canada and the USA[5], with very good results.

In 2017, we designed our own FLS unit which, for the moment, is focused on patients from orthogeriatrics (over 65 years with femoral fracture and/or pelvic branches). The FLS is made up of all the health professionals who will intervene throughout the acute hospitalization process, recovery process and subsequent follow-up (rehabilitation doctor, geriatrician, rheumatologist, traumatologist, maxillofacial, nurse, physiotherapist and occupational therapist).

All patients over 65 years of age who have suffered a fracture of the femur or pelvic branches are assessed by the ortho-geriatrics unit (excluding periprosthetic or metastatic). On the fifth day of admission to the traumatology unit they are transferred to hospital, where they will complete the rehabilitation and convalescence process. The rheumatologist indicates the pharmacological treatment for the secondary prevention of osteoporosis, after a maxillofacial evaluation. All our FLS patients are treated with calcium and vitamin D supplements, depending on the analytical values determined at admission (urea, creatinine, calcium, phosphate, 25-OH cholecalciferol, PTH and total proteins) and the comorbidities, such as renal failure. If the Barthel ADL prior to the fracture was greater than or equal to 60 and there was no severe cognitive impairment (GDS scale equal to or less than 3), the study was extended with a spine x-ray and a rheumatology inter-consultation.

During 2018, a total of 200 patients were assessed; 161 had a fractured femur and 39 of pelvic branches. 77% were women; mean age 85 years in both sexes with a range in women aged 65 to 103 and in men aged 69 to 96. Women were the majority (74%) in the subgroup of patients older than 90 years (representing 24% of the total) which was noteworthy. In all, 28% of the patients had a Barthel prior to the fracture was <60 and had no cognitive impairment, or if so, it was with a GDS <3. All patients had a specific pharmacological treatment for osteoporosis. The main reasons for exclusion from drug treatment were previous dementia (41%) and functional limitation (34%). Of the total of 200 patients who were assessed at the unit, only 15 had a previous diagnosis of osteoporosis and underwent or had undergone specific treatment.

In conclusion, we want to highlight that it is essential to ensure that the different assistances, primary, hospital and socio-health care, are coordinated to address the patient with fragility fracture, although it is very complex to properly bring together the different care levels. There are different FLS modalities and each health region can design it according to the needs and peculiarities of each territory.

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