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Sociedad Española de Investigación Ósea y del Metabolismo Mineral

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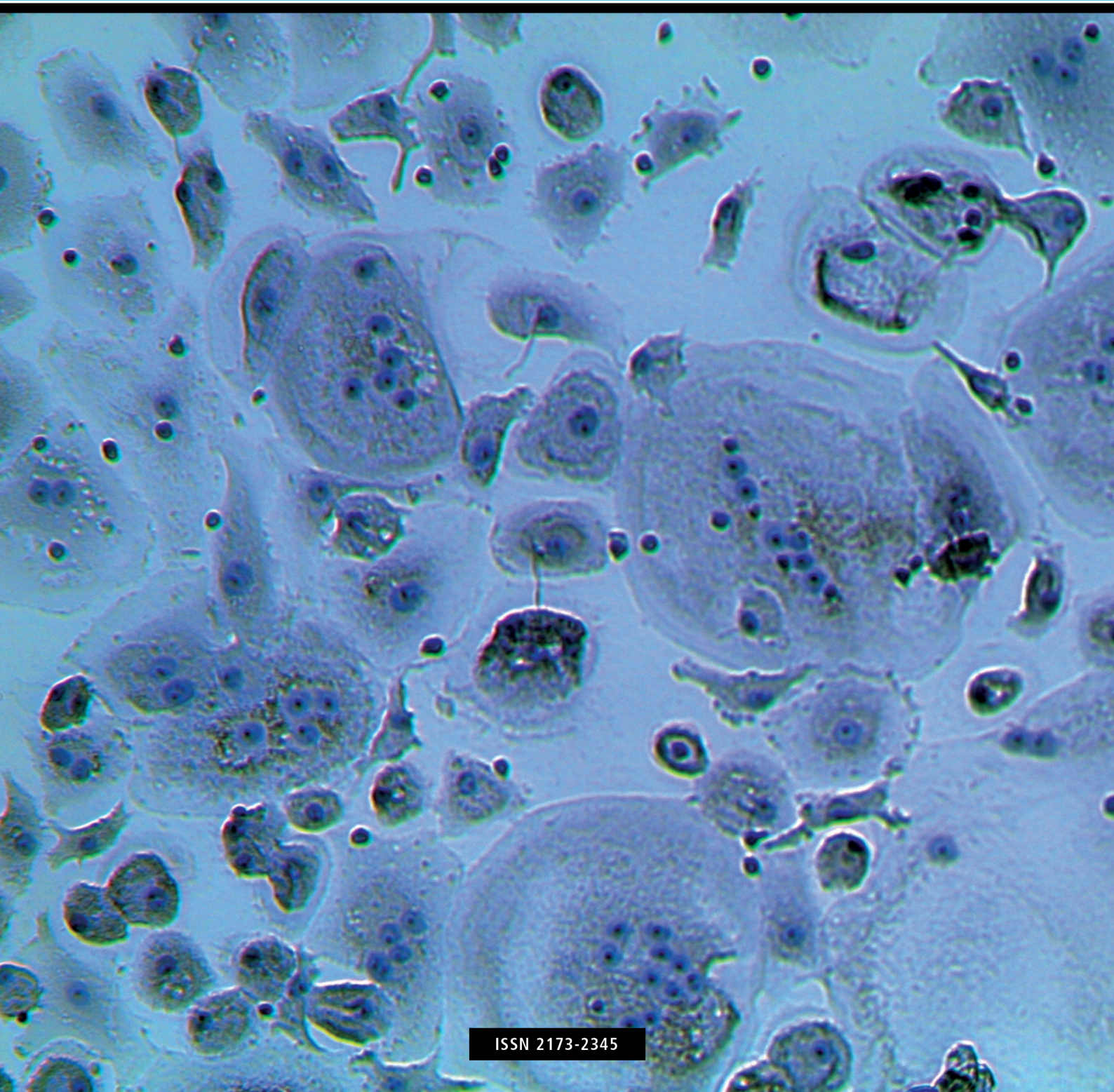
Fundación Española de Investigación Ósea y del Metabolismo Mineral

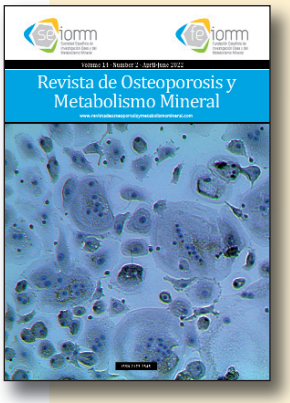
Volume 14 · Number 2 · April-June 2022

Revista de Osteoporosis y Metabolismo Mineral

www.revistadeosteoporosisymetabolismomineral.com



ISSN 2173-2345



Our cover: Human osteoclasts obtained by differentiation of peripheral blood precursors.
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Summary

Vol. 14 - Nº 2 - April-June 2022

Indexed in: Scielo, Web of Sciences, IBECS, Scopus, SIIC Data Bases, embase, Redalyc, Emerging Sources Citation Index, Open J-Gate, DOAJ, Free Medical Journal, Google Academic, Medes, Electronic Journals Library AZB, e-revistas, WorldCat, Latindex, EBSCOhost, MedicLatina, Dialnet, SafetyLit, Mosby's, Encare, Academic Keys, ERIH plus, British Library, ROAD.

Revista de Osteoporosis y Metabolismo Mineral has recently been acepted for coverage in the Emerging Sources Citation Index, wich is the new edition of the Web of Science that was launched in november 2015. This means that any articles published in the journal will be indexed in the Web of Science at the time of publication.

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ISSN: 2173-2345

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Rev Osteoporos Metab Miner. 2022;14(2):67-68

Familial hypocalciuric hypercalcemia. Concerning two cases

DOI: http://dx.doi.org/10.4321/S1889-836X2022000200001

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Date of receipt: 23/07/2021 - Date of acceptance: 11/01/2022

Familial hypocalciuric hypercalcemia (FHH) is a syndrome characterized by the association of mild or asymptomatic hereditary hypercalcemia and hypocalciuria. 3 subtypes have been described (FHH1, FHH2 and FHH3). FHH1, the most common, is due to inactivating mutations in the calcium-sensitive receptor (CaSR) gene[1-3]. Its prevalence is low, the inheritance is autosomal dominant, and it is often diagnosed by chance, because it is rarely symptomatic. Due to its clinical benignity, it is essential to establish a differential diagnosis (DD) with primary hyperparathyroidism (PHPT) to avoid unnecessary examinations and treatments. Routine genetic testing is not accurate because biochemical tests usually establish the diagnosis[4].

Two cases of FHH1 are described. In one, the need for a genetic study is debatable. In the other, the mutation found had not been previously described.

The first, a 47-year-old woman, consulted for mild hypercalcemia. With no relevant medical history or semiology of hypercalcemia, she had mild hypercalcemia with normal intact parathyroid hormone (iPTH), but the diagnostic study was not completed due to non-appearance during the following three years. Referred again by elevated iPTH, tests were requested to rule out PHPT. The results confirmed the persistence of hypercalcemia with slightly elevated iPTH and normal vitamin D, but without hypercalciuria (urine calciuria 24 hours 159.25 mg/24) (table 1). The cervical ultrasound and scintigraph scan did not reveal pathological data at the parathyroid level. The patient reported, at that time, that her mother and 2 of her 6 siblings had FHH due to a mutation in the CaSR gene. The genetic study of the patient confirmed the existence of the same CaSR mutation as her relatives: change c.1394G>A; P. (ArgRG465Gln).

Table 1. Biochemical data of the cases

	Creatinine (0.5-1.1) (mg/dl)	Total calcium (8.7-10.4) (mg/dl)	Phosphorus (2.7-4.5) (mg/dl)	Magnesium (1.7-2.4) (mg/dl)	iPTH (12-72 pg/ml)	25OHD (31-80 ng/ml)	Ca/Cr ratio (0-0.22)	CCCR	Calcium in urine of 24 h. (100-300 mg)
Case 1									
2011	0.67	10.6	2.9	–	43.2	24.9	–	–	
2014	–	10.1	2.9	–	92.3	ND	–	–	
2015	0.56	11.1	3.3	–	77	26.63	0.14	0.0114	159.25
2016 (1)	0.65	10.3	2.9	2.3	83.4	45.2	0.2	0.009	263.25
Case 2									
2008	1.2	10.7	3.5	2.4	–	23	–	–	77
2012	0.77	10.8	2.7	2.2	30.6	37.6	–	–	168
2017 (2)	0.78	10.9	2.6	2	49.6	50.9	0.04	0.003	75.08
2020	0.83	11.3	3.1	2.2	64.3	28.33	0.07	0.006	169.6

iPTH: intact parathormone; 25OHD: 25-OH vitamin D; CCCR: calcium/creatinine clearance ratio (index). (1) and (2) at that time were on calcifediol treatment.

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The second is a 36-year-old man referred for hypercalcemia, treated with oral corticosteroids (dexamethasone 0.5 mg/day, in recent years) for non-classical congenital adrenal hyperplasia. No other personal or family history of interest or semiology was attributable to hypercalcemia. He had mild hypercalcemia, a normal iPTH concentration, and a "normal" 24-hour calciuria (low for the calcaemia level), which has remained practically stable, with some clear hypocalciuria, during follow-up (table 1). He was diagnosed with lumbar osteopenia, which was considered secondary to chronic corticosteroid therapy. The genetic study, carried out in 2013, found a genetic mutation c.164dupC (p. Glu56Glyfs * 9) in exon 2 of CASR in heterozygosity. This alteration had not been described up to that date.

It is very uncommon for patients with FHH to present the most common symptoms in other hypercalcemic syndromes, even when the calcemia is higher. While slight elevations in bone turnover markers can be detected, this does not affect bone mineral density or increase the incidence of fractures. Hypercalcemia in patients with FHH is barely elevated, although in some family groups it can exceed 12 mg/dL, due to the peculiarities of the mutation present in CaSR[5], it is already present at birth, unlike PHPT, and persists throughout life.

Typically iPTH is inappropriately normal for calcium concentration, but occasionally it may be significantly elevated. In this case, DD with a PHPT is difficult. The other defining characteristic of the disease is excessive tubular calcium reabsorption despite hypercalcemia, which translates into a calcium/creatinine clearance ratio (CCCR) of less than 0.01 in 80% of cases. Most PHPT have a higher index (> 0.02)[6]. These low clearance rates in FHH persist even after complete parathyroidectomy, suggesting that calcium reabsorption is independent of PTH. CCCR has been proposed as a simple diagnostic test for a rapid DD between FHH and PHPT, taking as a cut-off point for FHH a value <0.02; but low CCCR values (between 0.01 and 0.02) have been observed in some typical PHPT, especially in those who concomitantly present with hypovitaminosis D or renal failure[7].

Therefore, genetic analysis continues to be the "gold standard" test to establish this DD. The genetic study is widely accepted for those patients with a CCCR <0.02[8,9], although some also limit the indications to children under 10 years of age with hypercalcemia and elevated or normal PTH, atypical cases that do not present hypocalciuria or with a phenotype of FHH with normocalcemic parents (de novo CaSR mutation), cases in which there are other relatives with hypercalcemia with no known cause and when there are no family members available for testing[10]. The indication for the genetic study is not always easy, as shown in the first case, in which the family history would have allowed a reliable diagnosis to be established with biochemical tests, but the repeated detection of elevated iPTH and the absence of hypocalciuria influenced the decision to perform genetic analysis.

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

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Rev Osteoporos Metab Miner. 2022;14(2):69-73

Joint recommendations on the management of patients with osteoporosis and/or fragility fractures during and after the pandemic due to COVID-19 of SEIOMM, SEFRAOS, SER, SEMI, SEGG, SEMG, SEMERGEN and SEEN

DOI: http://dx.doi.org/10.4321/S1889-836X2022000200002

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Date of receipt: 04/11/2021 - Date of acceptance: 08/11/2021

Introduction

The COVID-19 pandemic has impacted the healthcare of patients with osteoporosis and fragility fractures[1].

Some strategies aimed at protecting against the spread of the virus, such as social distancing, have brought about changes in care models that are been homogeneous in all areas.

The need to limit access to health centers and infections has imposed a system of telemedicine[2] which offers many advantages to professionals and users and has become a key assistance tool to ensure social distancing. Likewise, telematic consultation can have additional applications in routine clinical practice, as it allows medical professionals to attend to patients with displacement problems and efficiently solve doubts and/or problems related to treatment, so it could be especially useful to control therapeutic compliance. However, in order to advance more effectively and secure telematic attention, always seeking the greatest agility in the responses, it should be protocolized.

Based on the joint recommendations of the American Society for Bone and Mineral Research (ASBMR), American Association of Clinical Endocrinologists (AACE), European Calcified Tissue Society (ECTS) and National Osteoporosis Foundation (NOF)[3], a multidisciplinary group of experts from SEIOMM, together with those of other scientific societies (SEFRAOS, SER, SEMI, SEGG, SEMG, SEMERGEN and SEEN), has prepared this docu-

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ment to establish a series of recommendations in the diagnosis, treatment and follow-up of patients with osteoporosis and/or osteoporotic fragility fracture during and after the COVID-19 pandemic in Spain.

Healthcare recommendations

First visit

The first outpatient visit of patients with osteoporosis and/or fragility fractures, both in hospital and in primary care, should preferably be done in person if health circumstances permit. If the face-to-face visit is not possible, it should be carried out electronically (telephone and/or videoconference) without delaying patient care, trying to schedule a face-to-face visit as soon as possible.

In patients with fractures of the femur, vertebra, pelvis and humerus who require hospital admission, it is advisable to carry out the first clinical evaluation in the same admission, as well as to establish the primary care link prior to discharge, to agree on treatment and ensure follow-up and adherence through liaison staff or case manager, when possible.

Follow-up visit

Follow-up can be carried out in person or telematically (telephone/videoconference), depending on the existing health recommendations at the time and the patient's profile.

Telematic follow-up visits should be systematic and protocolized[4], and scheduled in pre-selected patients in advance, after reviewing the clinical history by the assigned physician, whenever possible.

Profile of candidate patient for the telematic consultation:

- Patient previously assessed, in at least one previous face-to-face visit.
- That does not present signs or symptoms that require a directed physical examination.
- That does not present auditory, cognitive or functional problems (unless there is the possibility of another cohabitant interlocutor).
- That does not express refusal to a telecare model.
- That they have access to a fixed or mobile telephone line.
- That present displacement problems.

The steps to follow in the telematic consultation would be:

1. Initial contact with the patient, through administrative staff/case management days before the consultation: locate the patient, inform the patient of the day and time, give a series of recommendations for which visit is more fluid: arrange of the treatment carried out, family member of help in case it is necessary, remember to carry out complementary tests prior to the visit if necessary.
2. Telematic medical consultation using the same system as in the face-to-face visit.
3. Care circuit: request for tests or new consultation if appropriate.
4. Patient flow: through administrative/case management staff.

Recommendations in complementary tests

Lab tests

To reduce the number of trips to a health center, the essential laboratory procedures should be carried out.

It is recommended to perform analytics in the first patient evaluation, whenever possible, prior to the start of treatment, especially if a drug is used parenterally (zoledronic acid, denosumab, teriparatide or romosozumab *).

In the follow-up of the patient, it is recommended to carry out the analytics that, depending on the characteristics of the patient and his pathology, are necessary at the physician's discretion.

Imaging tests

Imaging tests (radiography, computerized axial tomography, magnetic resonance imaging or scintigraphy) should be restricted to cases in which the presence of an osteoporotic fragility fracture or other processes that require a medical history and/or physical examination is suspected differential diagnosis.

In the patient's first visit it is convenient to check if there are chest or spinal radiographs performed previously to investigate the presence of previous vertebral fractures.

Bone densitometry should be restricted to those cases in which it is necessary for making a therapeutic decision. In all other situations, when sanitary circumstances are not favorable, its performance could be postponed.

Recommendations in non-pharmacological treatment

It is recommended, especially during periods of confinement or restricted mobility, to encourage patients to engage in daily, weighted physical exercise, such as walking around the house or going up and down stairs.

Efforts should be made to avoid falls, controlling polypharmacy, and following the recommendations set out in the consensus document on the prevention of frailty and falls in the elderly of the Ministry of Health[5].

The patient should be insisted on avoiding toxic habits such as smoking or drinking alcohol, maintaining a healthy diet with sufficient protein and calcium intake, without forgetting adequate sun exposure.

Recommendations in pharmacological treatment

General recommendations

Care should be taken to not delay the initiation of fracture prevention pharmacological treatment (antiresorptive or anabolic) in patients at high risk of fracture, especially in those who have suffered a recent fracture (imminent risk of fracture).

There is no evidence osteoporosis treatment increases the risk or severity of COVID-19 infection or alters the course of the disease[6]. However, some thromboembolic complications have been described in infected patients[7,8], so it is prudent to avoid the prescription of estrogens or SERMs (raloxifene, bazedoxifene) in these patients or to temporarily interrupt their administration during COVID-19 infection.

It is recommended, both at the time of the first prescription and at all follow-up visits (in person or online) to remind the patient of the importance of good adherence to treatment.

In patients with low calcium intake in whom it is not possible to increase it through diet, it is recommended to administer supplements, without exceeding 1,200 mg/day.

Patients with osteoporosis and a 25-hydroxyvitamin deficiency or at risk of deficiency should receive treatment with cholecalciferol or calcifediol, with the aim of

not marketed in Spain at the time of writing up this document.

maintaining levels between 30-50 ng/ml[9].

Although there is insufficient evidence to recommend vitamin D treatment for the prevention or treatment of COVID-19, several published studies suggest a better course of the disease in patients who achieve 25-hydroxyvitamin D levels >30 ng/ml[10,11].

Specific recommendations for subcutaneous injectable treatments

Denosumab: Good adherence must be ensured and administration discontinuation or delay should be avoided, as a "rebound" effect may occur after discontinuation, with a marked increase in bone turnover, accelerated loss of bone mineral density[12,13] and in some patients, an increased risk of multiple vertebral fractures[14]. Therefore, it is recommended to confirm the patient's adherence to treatment at each visit.

Teriparatide and romosozumab: Keep in mind the importance of good adherence and correct administration of treatment at each visit.

It is convenient to remember that all subcutaneous treatments for osteoporosis have specific patient support programs for each drug through which they can receive information for its correct administration.

When health and/or patient circumstances make it difficult to administer denosumab or teriparatide, it is recommended to assess the possibility of self-administration assisted by tutorial videos. If this is not possible, and depending on the characteristics of the patient and the possibilities, it is recommended to administer an infusion of zoledronic acid as soon as possible[15] or to prescribe treatment with oral bisphosphonates (alendronate or risedronate).

Specific recommendations for intravenous treatments for osteoporosis (zoledronic acid)

It should be remembered that treatment with zoledronic acid may cause, mainly after the first dose, a flu-like side effect that could be confused with mild COVID-19 symptoms.

In patients at high risk of fracture, especially those with a recent fracture, it is recommended not to delay the initiation of zoledronic acid treatment. In cases where the administration of a first dose of zoledronic acid is not possible due to health circumstances, it is recommended to prescribe denosumab or oral bisphosphonates based on the characteristics of the patient and their risk of fracture (table 1).

Since bisphosphonates have a residual effect that is maintained for months, or even years, on the skeleton after their administration[16-19], the successive administration of zoledronic acid could be delayed for a few months when health circumstances make it difficult for the patient to access the hospital. However, if this situation is prolonged, it is advisable to assess the prescription of oral bisphosphonates or denosumab, depending on the characteristics of the patient and their risk of fracture.

Table 1. Recommendations for the administration of the vaccine against COVID-19 according to the treatment for osteoporosis[3]

Treatment	Recommendations
Oral bisphosphonates	Continue your administration
Intravenous bisphosphonates	Space 7 days between administration and the vaccine
Denosumab	Space 4-7 days between administration and the vaccine. If both are administered in a shorter period of time, use the contralateral arm or an alternative site
Teriparatide	Continue its administration
Romosozumab*	Space 4-7 days between administration and the vaccine
Raloxifene/Bazedoxifene	Continue administration

* not marketed in Spain at the time of writing up this document.

Rehabilitation treatment

The home confinement imposed during the pandemic in most countries has led to a change in routines and a decrease in physical activity of our elderly, which translates into a loss of strength and muscle mass and, consequently, in a greater risk of falls and fractures[20].

Thus, it is essential to recommend the patient carry out regular physical activity adapted to each situation. It will be important to provide information to be able to perform this activity at home, in the event that the authorities indicate periods of confinement.

Recommendations of physical activity for frail older people and those at risk of falls

The most beneficial type of physical exercise in the frail elderly is the so-called multicomponent training, which combines strength, endurance, balance and gait training and is the one that has been shown to be the most effective in the recovery/improvement of functional capacity. The Vivifrail Multicomponent Physical Exercise Program (www.vivifrail.com) tries to provide the necessary knowledge for the prescription of physical exercise in the prevention of frailty and the risk of falls in the elderly[21].

This program makes it possible to assess the degree of frailty and the risk of falls, and provides recommendations for physical exercise adapted to the condition of the person evaluated. It also has graphic and visual material on directed physical activity to carry out at home.

Recommendations for the control in the evolution of the fracture consolidation

For the clinical and radiological evolutionary control of the fracture consolidation, we must follow the specific recommendations of the traumatologist. In general, follow-up visits may be carried out in person or online depending on the patient's profile, the type of fracture, the type of treatment carried out, the need or not to carry out a radiological control and the existing health recommendations in the moment. We recommend that follow-up visits are always in person in those cases in which problems with wound healing or infection, joint stiffness or other complications related to the fracture are suspected[22].

Recommendations for the functional recovery of the patient who has suffered a fracture

In fragile patients who have suffered a fracture, mainly the hip, it is essential to continue with a rehabilitation program with the aim of improving functionality, and if possible, reaching the situation prior to the time of the fracture.

Among the tele-rehabilitation platforms there is the ACTIVEHIP+[23] educational program. This program offers advice and training to patients and caregivers to improve functional recovery, favoring the independence of the patient to carry out their daily activities and helping to improve their quality of life in general after having suffered a hip fracture. It is based on the implementation of a multicomponent exercise program and occupational therapy through the online platform and an app.

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

Decalogue of recommendations for the management of patients with osteoporosis and/or frailty fractures during and after the COVID-19 pandemic

1. **It is recommended that the first outpatient visit, both in hospital and in Primary Care, be preferably in person, if health circumstances allow it.**
2. **It is recommended that follow-up telematic visits be scheduled in pre-selected patients, after reviewing the medical history by the responsible physician, whenever possible.**
3. **It is recommended to carry out the minimum laboratory and imaging tests necessary for a correct diagnosis, in order to reduce the number of trips to a health center.**
4. **It is recommended, especially during periods of confinement or restricted mobility, to encourage patients to carry out daily physical exercise with load, avoid toxic habits and take appropriate measures to reduce falls at home.**
5. **It is recommended to prescribe cholecalciferol or calcifediol, if the patient has a 25-hydroxyvitamin D deficiency, due to the beneficial effects on his bone pathology and the possible effect on the evolution of the COVID-19 infection.**
6. **It is recommended not to delay the start of antiresorptive or anabolic treatment, especially in patients with high or very high risk of fracture.**
7. **It is recommended to insist on adherence to treatment, particularly with teriparatide and denosumab, due to the adverse effects of their discontinuation, especially denosumab.**
8. **It is recommended not to delay the first administration of zoledronic acid, either due to discontinuation of denosumab or for any other reason.**
9. **A time interval is recommended between the administration of denosumab, zoledronic acid, or romosozumab and the COVID-19 vaccine. In the case of zoledronic acid, it should also be taken into account that its administration can produce a flu-like syndrome that could be confused with the symptoms of COVID-19 infection.**
10. **It is recommended that patients who have suffered a hip fracture follow a rehabilitation program, with the aim of improving functionality, with access to tele-rehabilitation platforms.**

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Rev Osteoporos Metab Miner. 2022;14(2):74-81

Clinical efficacy of FRAX®-based hybrid and age-dependent intervention thresholds in the Ecuadorian population

DOI: http://dx.doi.org/10.4321/S1889-836X2022000200003

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Date of receipt: 28/01/2021 - Date of acceptance: 21/03/2022

Summary

Objetive: To assess the clinical impact of FRAX-based intervention thresholds in Ecuadorian women. Also to test a combination of fixed and age-specific intervention thresholds to optimize the selection of women eligible for intervention.
Patients and methods: Transversal study in which 2,283 women aged 60 to 94 years were selected. We calculated the risk of major osteoporotic and femoral neck fractures with the Ecuadorian FRAX model (version 4.1), and calculated the proportion of individuals eligible for treatment and bone mineral density assessment applying age-specific thresholds of 60 to 94 years and a fixed threshold from 75 years.
Results: Applying age-specific thresholds, 2% of women qualified for treatment and 73.7% for bone mineral density assessment. Depending on age, women eligible for treatment ranged from 0.7 to 3.8% and those eligible for bone mineral density evaluation from 58.3 to 80.5%.
With the fixed threshold, 31% of women qualified for treatment and 76.3% for bone mineral density assessment. Depending on age, women potentially eligible for treatment ranged from 3.8% to 76.5%, and those eligible for bone mineral density assessment from 65.2% to 85.4%.
Conclusions: The proportion of women potentially eligible for treatment is low compared to countries with a high risk of fractures. Using a fixed threshold starting at age 75 optimizes the proportion of women eligible for treatment. In low to moderate fracture risk countries with limited resources, a hybrid model may be more appropriate.

Key words: FRAX, intervention threshold, hybrid threshold, fracture risk, Ecuador.

Introduction

Osteoporosis is a skeletal disorder characterized by compromised bone strength that predisposes to an increased risk of fracture[1]. Osteoporosis-related fractures are a major health problem and a significant economic and social burden worldwide. By 2050, 12.5% of hip fractures worldwide are projected to occur in the Latin American and Caribbean region[2]. Consequently, it is very important to recognize and treat people who are at high risk of fractures, for which several simple and inexpensive alternatives have been developed to identify and select people at risk who are candidates for treatment and evaluation of bone mineral density (BMD)[3].

The National Osteoporosis Foundation (NOF) recommends the FRAX tool for use in patients with osteopenia to identify subjects at high risk of osteoporotic fracture who are eligible for intervention[4]. On the other hand, the National Osteoporosis Guideline Group (NOGG) recommends the FRAX tool to identify the age-specific fracture risk in each country to choose treatment candidates and recommend BMD measurement[5].

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Fracture probability differs significantly in different regions of the world[6]. Thus, the FRAX model for a given country (or ethnic group) must be individualized based on the epidemiology of fractures and the population's life expectancy[7,8]. So it is important to establish appropriate intervention thresholds (treatment and recommendation to measure BMD) for each country or population[9]. In 2018, Clark et al. published FRAX-based intervention and evaluation thresholds for seven countries in the Latin American region: Argentina, Brazil, Chile, Colombia, Ecuador, Mexico, and Venezuela[10].

A FRAX model for Ecuador was released in 2012[11,12], but recently, the model has been revised and modified using more current fracture and mortality rates[13,14]. In 2019, the new age-specific evaluation and treatment thresholds for the population of Ecuador were announced[15].

The age-specific intervention thresholds obtained according to the NOGG strategy are hindered by underestimating the risk of fracture at older ages and overestimate it at younger ages[16]. As a means of overcoming this drawback, McCloskey proposed the use of alternative thresholds, which combine age-specific thresholds up to 70 years and thereafter a fixed threshold with a single probability of fracture in all age groups[16]. This strategy has also been implemented by other authors who have stated that the use of hybrid thresholds could be appropriate in countries where the incidence of hip fractures is low, as is the case in some countries in the Middle East, southern Europe and Latin America[17-19].

In Latin America, the clinical efficacy of these thresholds to identify candidates for intervention in the respective populations has not been determined to date. In this study, we performed an analysis of the effectiveness with which the probability of fracture obtained with the Ecuadorian FRAX model (without BMD) identifies women who would be candidates for treatment for the calculation of FRAX probabilities in the absence. Additionally, we tested a combination of age-specific and fixed intervention thresholds to optimize the selection of women eligible for treatment and referral for BMD assessment.

Methods

Population

The present study used data from participants in the National Survey of Health, Well-being and Aging (SABE)[20]. This survey is a probability sample of households with at least one person aged 60 years or older residing in the Andean and coastal region of continental Ecuador (only the insular territory and the Amazon were excluded due to their lower population density, 4.4%), making it a representative sample of the Ecuadorian population. The data and the methodology of the survey (inclusion and exclusion criteria, sample size calculation, statistical methods), including the operation manuals, are freely accessible and available to the public at http://www.ecuadorencifras.gob.ec/encuesta-de-salud-bienestar-del-adulto-mayor/[20].

A total of 2,377 women over the age of 60 participated in the national SABE survey. Complete interview information was available for 2,283 women.

A structured questionnaire was used to collect information from all participants and was used to provide risk variables for the calculation of FRAX probabilities in the absence in the absence of BMD.

Age and sex were self-reported. Height in centimeters and weight in kilograms were measured and body mass index (kg/m^2) was calculated. Smoking status was classified as current, former and never. Mean alcohol consumption per week over the previous three months was classified as none, one day, or two or more days per week. Forearm and hip fractures within the past year were self-reported. In the SABE survey, participants were asked: Have you fallen in the last year? Have you suffered a fracture when you fell? Have you broken your hip in the last year? Have you broken your wrist in the last year? so we assumed that they were fragility fractures. Because the SABE[20] survey does not collect data on long-term use of glucocorticoids or family history of fractures, a negative response ("no") was entered in the FRAX questionnaire for both factors. Each participant provided informed consent prior to her inclusion in the survey[20]. The use of SABE survey data is freely accessible and, in accordance with local legislation, authorization is not required to use it, provided that the anonymity of the participants is preserved. The ethics committee of the "Abel Gilbert Pontón" hospital in Guayaquil, Ecuador, authorized the protocol and carrying out of this study.

Statistical analysis of the data was carried out with the EPIDAT Version 4.2 computer program[www.sergas.es/Saude-publica/EPIDAT].

Intervention thresholds

To establish intervention thresholds and assess bone mineral density (BMD), the methodology adopted by the NOGG in the FRAX-based guidelines for the United Kingdom was used[21].

The number of women aged 60 years or older who exceeded the intervention threshold (and would therefore be eligible for treatment) was calculated as a total and in 5-year age intervals using FRAX probabilities (BMD not included in the calculation).

As the NOGG considers a prior fracture to carry sufficient risk to recommend treatment, the threshold for intervention in women without a prior fracture was set at the 10-year (age-specific) probability of sustaining a major osteoporotic fracture (hip, spine, forearm, or humerus) equivalent to that of women with a previous fragility fracture using the Ecuadorian FRAX model (version 4.1). Body mass index was set at 25 kg/m^2.

Evaluation thresholds to recommend measuring BMD

Two evaluation thresholds were considered to formulate recommendations for the measurement of BMD[21]. Lower Evaluation Threshold (LET): Level of probability below which neither treatment nor a BMD test should be considered. Upper Evaluation Threshold (UET): Probability level above which treatment can be recommended regardless of BMD.

The lower evaluation threshold was established to exclude the requirement to measure BMD in women without clinical risk factors as indicated in the European guidelines[21]. An upper threshold was chosen to minimize the likelihood that an individual identified as being in a high-risk category (based solely on clinical risk factors) might, with additional BMD information, be reclassified into a low-risk category. The upper evaluation threshold was set at 1.2 times the intervention threshold[21].

Fracture probabilities
The probabilities in the next 10 years of suffering a major osteoporotic fracture (MOF) and a hip fracture were calculated using the Ecuadorian FRAX model (version 4.1)[15]. There was no confirmed diagnosis of secondary osteoporosis and rheumatoid arthritis (RA), so these data were recorded as "NO", following the recommendations of the FRAX questionnaire. Calculations did not include BMD. The upper age limit for probability calculation with FRAX is 90 years.

Evaluation strategy
The strategy for establishing BMD measurement and intervention thresholds followed the FRAX-based methodology, approved by the NOGG in the United Kingdom[22] and later recommended by the European guidelines[23].

Women with a prior fragility fracture are considered eligible for treatment without further assessment. In women without a previous fragility fracture, the strategy was based on the evaluation of the probability in the next 10 years of suffering a MOF. Women with probabilities below the lower assessment threshold were not considered eligible for treatment or BMD assessment. Women with probabilities above the upper evaluation threshold were considered eligible for treatment. Women with probabilities between the upper and lower limits of the assessment threshold would be referred for BMD measurement and re-assessment of fracture risk.

Results
A total of 2,377 women over the age of 60 participated in the SABE survey. 94 had a previous fracture and were excluded from the analysis. Complete interview information was available for 2,283 women.

The 2283 women (without previous fractures) had a mean age of 70.9 (7.9), and a body mass index (BMI) of 27.3 (7.8) kg/m^2; 61 (26.7%) were current smokers and 275 (12%) were former smokers; 16 (0.7%) drank alcohol 2 or more days per week.

Thresholds
The intervention and evaluation thresholds specific to the Ecuadorian population and the methodology used to obtain them have been described in a previous publication[15] and are presented in table 1 and figure 1.

The intervention threshold in women increased with age, from a 10-year probability of major osteoporotic fracture of 1.8% at age 60 years to 12% at age 90 years (table 1).

Table 1, figure 1 also provides age-specific upper and lower evaluation thresholds for recommending BMD measurement. At age 65, for example, BMD testing would not be recommended in an individual with a fracture probability of less than 1.3%. At the same age, a BMD test with a probability of fracture between 1.3 and 3.12% would be recommended. Treatment without the requirement of a BMD test would be recommended in individuals with a fracture probability greater than 2.6%.

FRAX score
The mean 10-year probability of having a MOF was 2.85 (2.3) but ranged from 0.92 (0.22) to 7.46 (1.25) depending on age; and the mean 10-year probability of a hip fracture was 1.21 (1.43), but ranged from 0.19 (0.15) to 4.25 (1.29) depending on age.

Impact
Age-Specific Intervention Thresholds
The proportion of women eligible for treatment was lower at older ages (80 years and older), and on average 2% of the female population aged 60 years or older exceeded the intervention threshold and were therefore eligible for treatment. Depending on age, the proportion of women potentially eligible for treatment ranged from 0.7 to 3.8%.

On average, the proportion eligible for evaluation with BMD is 73.7%, but it varied from 58.3 to 80.5% depending on age.

The impact of intervention and assessment thresholds (age-specific) is presented in table 2.

Fixed Intervention Threshold (hybrid or alternative)
Because the age-specific intervention threshold would be too high to include some older people, we also chose a fixed threshold, which was set at the 10-year probability of having an MOF of 6.8% for the population of 75 years and older (table 2, figure 2).

The proportion of the female population aged 75 years and older eligible for treatment was higher at older ages, and on average 31.4% of women aged 75 years and older exceeded the intervention threshold and were therefore eligible for treatment. Depending on age, the proportion of women potentially eligible for treatment ranged from 3.8 to 76.5%. On average, the proportion of women eligible for BMD evaluation is 76.3%, but ranged from 65.2 to 85.4% depending on age. The impact of fixed intervention and evaluation thresholds are shown in table 2 and figure 3.

Discussion
Our study establishes the efficiency with which the intervention thresholds obtained with the Ecuadorian FRAX model (version 4.1) allow us to quantify the proportion of subjects eligible for intervention in our population. In addition, we tested the use of a "fixed" (hybrid) threshold starting at age 75 to optimize treatment choice in older women.

In a previous publication, we described the age-specific fracture probabilities based on the FRAX model, as well as the treatment thresholds and BMD evaluation for our country[15]. We used the intervention thresholds approach used by the NOGG in the United Kingdom[5,19], but applied to the Ecuadorian FRAX model[15].

The setting of intervention thresholds varies considerably around the world, with guidelines using fixed or age-specific thresholds and sometimes combining a probability threshold with BMD in the osteoporotic range[19,24,25].

The WHO suggests that each country determine its own intervention thresholds based on its own epidemiology and socioeconomic characteristics[26]. International clinical guidelines also take these epidemiological differences into account. Consequently, recommendations for treatment differ between countries. The only tool that considers these epidemiological differences between countries is FRAX, which is reflected in the calculation of the probability of fracture risk[8,28].

The age-specific intervention threshold, developed by the NOGG[22], is mainly used in the United Kingdom and varies according to age and sex, being higher in older ages[27] so inequalities arise in access to treatment, especially in older ages to 70 years[28]. An alternative threshold using a hybrid model reduces this disparity[19].

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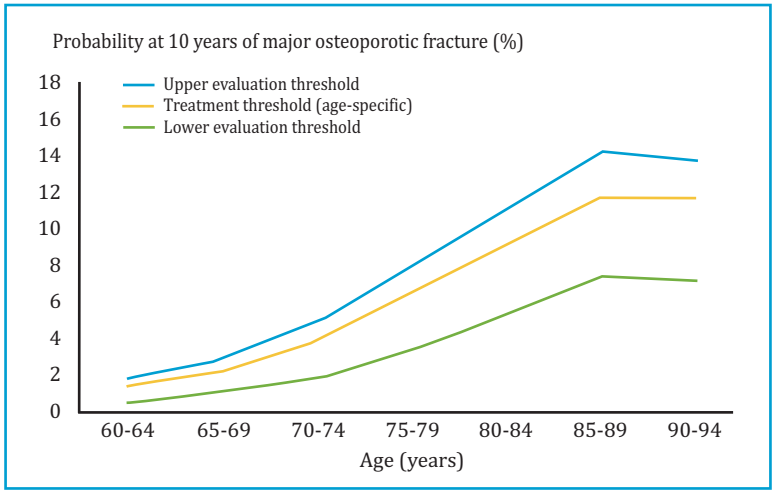
Table 1. Treatment thresholds and evaluation of BMD based on the Ecuadorian FRAX* model[15]

	Major fractures			Hip fractures		
Age group	Treatment threshold	Lower evaluation threshold	Upper evaluation threshold	Treatment threshold	Lower evaluation threshold	Upper evaluation threshold
50-54	1.2	0.6	1.4	0.2	0	0.2
55-59	1.4	0.6	1.7	0.2	0.1	0.2
60-64	1.8	0.8	2.1	0.4	0.1	0.48
65-69	2.6	1.3	3.1	0.7	0.3	0.8
70-74	4.3	2.2	5.16	1.3	0.6	1.56
75-79	6.8	3.7	8.16	2.4	1.3	2.9
80-84	9.5	5.7	11.1	4.0	2.6	4.8
85-89	12	7.6	14.4	5.9	3.8	7.0
90-94	12	7.3	14	5.6	3.6	6.7

BMD: bone mineral density; * Version 4.1.

Figure 1. Age-specific BMD intervention and evaluation thresholds in Ecuador. The yellow line represents the intervention threshold (age-specific). The blue and green lines represent the upper and lower evaluation thresholds[15]



In a systematic review, Kanis et al. describe the intervention thresholds of various populations, and observe significant differences between countries with different treatments and health cost reimbursement systems[19]. In the United Kingdom, the intervention threshold is globally 7%, although it varies with age[21]. The highest threshold corresponds to the USA, where it is 20% for a major osteoporotic fracture and 3% for a femoral fracture[19].

In countries with low incidence rates of hip fractures, lower intervention thresholds have been described compared to other countries such as the United Kingdom, the United States, and Canada[6,17,29]. For example, in Lebanon, age-specific intervention thresholds (using an approach similar to NOGG), were low, barely exceeding 5% at age 65 and less than 10% up to age 70 in women.

Unlike countries such as the USA, Canada, Japan, Australia and the United Kingdom, in which fixed intervention thresholds are used, in Latin America it was shown that it was better to establish age-specific intervention thresholds for each country[10]. However, the impact or effect of these thresholds on decision-making about treatment and/or assessment of BMD in Latin American countries has not been established.

In the latest UK guidelines[22], the intervention threshold up to 70 years of age is set at a risk equivalent to that associated with a previous fracture, and fixed thresholds are applied from 70 years of age or older. Thus, the proportion of women potentially eligible for treatment increases from approximately 30 to 50% depending on age[16]. In Lebanon, using an approach similar to the NOGG, the proportion of women aged 50 to 85 years who are eligible for intervention ranged from 11 to 18% in women without prior fractures[17], and using a fixed hybrid model, less than 5% of postmenopausal women without fractures would be eligible for treatment at age 65, and between 13 and 17% thereafter[17]. In a population-based study in Turkey, approximately 13.6% of the female population aged 50 years or older without a previous fracture would be eligible for treatment[30].

In the Latin American countries that have FRAX, intervention thresholds range between 1.2% (Ecuador) and 27% (Argentina)[10] depending on age and are generally lower than in developed countries. Thus, for example, in

Table 2. Women potentially eligible for treatment and evaluation of BMD (without fractures)

	Age-specific treatment threshold					Fixed treatment threshold				
Age group		Above the TT		Between the ET			Above the TT		Between the ET	
	N	n	%	n	%	N	n	%	n	%
60-64	595	4	0.7	479	80.5					
65-69	538	12	2.2	393	73.0					
70-74	458	12	2.6	344	75.1					
75-79	313	12	3.8	221	70.6	313	12	3.8	221	70.6
80-84	226	5	2.2	155	68.6	226	88	38.9	193	85.4
85-89	115	0	0	67	58.3	115	88	76.5	75	65.2
90-94	38	0	0	24	63.2	38	29	76,3	32	84.2
≥60	2,283		2		73.7					
≥75						692		31.4		76.3
	100%					30.31%				

TT: treatment threshold; ET: BMD evaluation threshold; BMD: bone mineral density.

the 5 main countries of the European Union (United Kingdom, Spain, Italy, France, and Germany), they range between 6.3 and 32.5% depending on age[19].

In the present study, age-specific intervention thresholds were low, ranging from 1.8% at 60 years to less than 5% at 74 years. From 75 years of age, intervention thresholds increased from 6.8 to 12% depending on age. These results reflect the low age-adjusted incidence rates of hip fractures in Ecuador compared to the 5 main countries of the European Union[6]. The proportion of women between 60 and 94 years old who exceed the specific age thresholds and are therefore eligible for treatment is 1.96%, but it varied between 0.67 and 3.83% depending on age. At younger ages (60 to 74 years), FRAX overestimates the number of women eligible for treatment (n=28) and underestimates it in older women (n=17).

Some concerns have been raised regarding the use of fixed, age-specific thresholds: the NOGG guideline may overtreat very low-risk (<10%) young patients and undertreat the elderly[27,34], while the NOF guideline treats the majority of the elderly with a greater use of resources[18].

Hybrid thresholds have been used in some countries[16,17,31-35]. In 2015, a hybrid model using an age-specific threshold up to age 70 and a fixed threshold of 20% thereafter was evaluated in the UK, allowing a higher proportion of older women to be eligible for treatment compared to the previous NOGG model[16].

Figure 2. Hybrid thresholds of treatment and evaluation of BMD. The yellow line represents the treatment threshold. Blue and green lines represent upper and lower evaluation thresholds

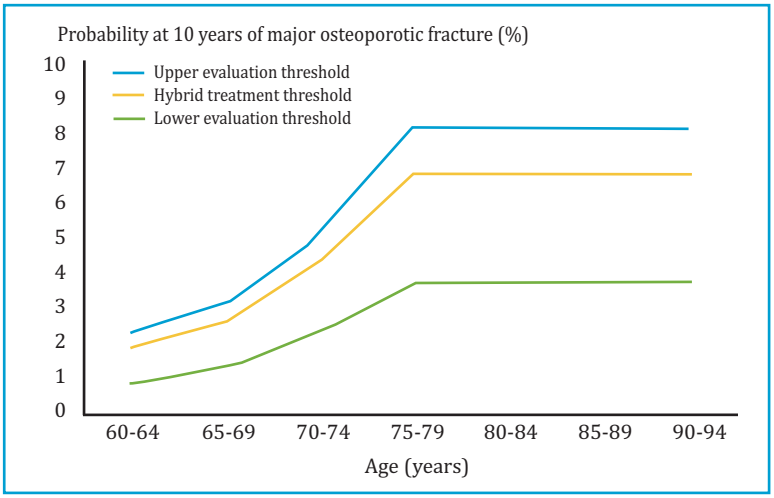
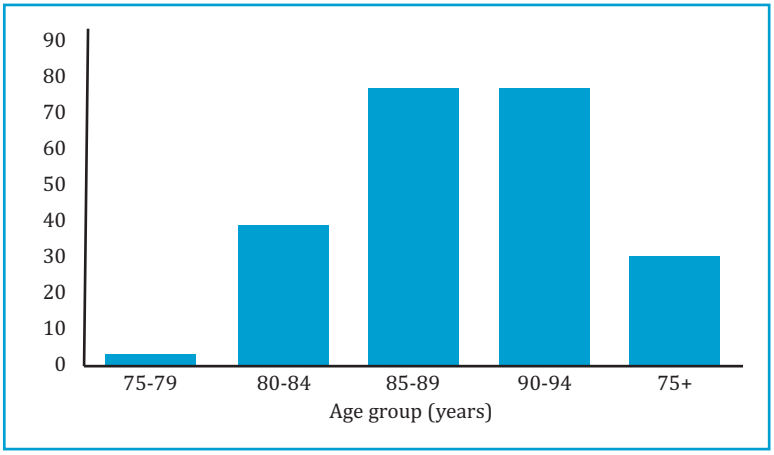


Figure 3. Proportion of women within each age group that would be recommended for treatment based on fixed thresholds



In Lebanon, the application of a hybrid model, a fixed threshold (10%) up to age 70 years and an age-specific threshold thereafter, avoids pharmacological treatment in a large proportion of younger subjects at low risk of fracture and directs it to elderly people at high risk[17].

The usefulness of the hybrid model has been suggested as potentially suitable for countries with low fracture rates, such as in the Middle East, southern Europe and Latin America[17,18]. For example, recently in a large clinical trial conducted in Latin American countries, the low incidence of fractures could not be explained exclusively by low BMD levels, but was consistent with low baseline FRAX scores[36,37].

Ecuador is a country with a low risk of fracture[13] similar to Brazil, Colombia, Chile and Venezuela in Latin America[37,38]. The low incidence of fracture is reflected in the low probabilities of fracture at 10 years calculated with FRAX described in this manuscript. Indeed, as we can see, the intervention thresholds are higher in the 5 main countries of the European Union (Spain, France, Italy, Germany and the United Kingdom) in which the incidence of hip fractures is higher[19], compared to the countries with a lower incidence of hip fractures[6,13].

The hybrid intervention threshold concept proposed in this study is similar to the application of the hybrid intervention threshold in the United Kingdom. However, in the present study, we found that a fixed intervention threshold was more suitable for participants older than 75 years, rather than 70 years. This fact is consistent with Kanis's suggestion that "fracture thresholds should be tailored individually on a country-by-country basis"[19].

In the SABE survey[20], 70% of women are under 75 years of age and 30% are 75 and over, so the decision to choose a new fixed intervention threshold was aimed at capturing the majority of women from 75 years and older[16]. In our analysis, the age-specific thresholds were very high from the age of 75 years and most of the patients could not reach them. The application of an age-specific threshold similar to that of NOGG up to 74 years, and a fixed threshold of 6.8% from 75 years, avoids the recommendation of pharmacological treatment in younger women at low risk, and directs them to favor of women at high risk. Consequently, it was decided that the intervention and evaluation thresholds would remain identical to those of the NOGG strategy until age 75 years, but thereafter a constant threshold would be maintained for older ages (i.e., the threshold at age 75 was applied to older ages)[16].

The NOGG guide establishes thresholds based on FRAX probabilities without BMD to select candidate patients to measure BMD[39], an upper evaluation threshold and a lower evaluation threshold. Those with intermediate probability values are referred for BMD evaluation. In general, use of the NOGG thresholds would identify between 6 and 20 percent of women as eligible for BMD measurement, depending on age[23].

Using age-specific thresholds, Ecuadorian women aged 60 years and older do not require BMD measurement if their probability of having an MOF at 10 years is less than 0.8%. Treatment (without BMD measurements) should be recommended if the 10-year MOF probability is greater than 1.8%. Finally, if this risk is 0.8 to 2.6%, additional BMD measurement and reassessment of fracture risk is required. With this approach, 58.3 to 80.5% (depending on age) of Ecuadorian women are eligible for BMD measurement. In the case of using the alternative threshold from 75 years of age, it turns out that 65.2 to 85.4% are eligible for BMD measurement.

The low values of the intervention thresholds in different developing countries, compared to the developed countries of the northern hemisphere, could be explained by the low incidence of hip fractures found among the former[6]. In a systematic review of the incidence of hip fractures worldwide, the 5 main countries of the European Union (United Kingdom, France, Italy, Germany and Spain) and the USA, are in the range of high risk of hip fractures. fractures according to the Kanis classification[38]. When comparing the probabilities of FRAX fracture (intervention thresholds) of these countries, it can be seen that in all of them they are higher than 15% (high risk)[5] than that of 7 countries in Latin America that have a FRAX model (Argentina, Brazil, Chile, Colombia, Ecuador, Mexico and Venezuela) with a lower incidence of hip fractures. Indeed, the 10-year probability of MOF in 4 of them is <10% and in another 2 it is <15% (Mexico and Chile), Argentina being the only exception with >15%[10,13,38].

This has also been described in countries in other regions, for example in Lebanon and Turkey where the results[17] reflect the low fracture incidence rates compared to other countries such as the UK, USA, and Canada[29,40]. This consideration could be applicable to other countries in the Middle East, with equally low fracture incidence rates[17].

Some limitations of the present study must be acknowledged. First, although the survey was large and representative of the Ecuadorian population, there were few women interviewed in the older age groups (17%), which could impair the accuracy of our estimates and therefore the number of women eligible for treatment.

BMD was not measured in the survey, which would have made it possible to improve the estimate of fracture risk, but this was not feasible in the context of the study. However, the probability of fracture calculated with and without BMD is the same as long as the population studied is truly representative of the general population[16]. The fractures were self-reported and were not confirmed by radiology, which could constitute a memory bias in the information collected. The SABE survey[20] only includes women of 60 years and older, so we do not cover the likelihood of fracture risk in people of younger ages (40-59 years).

We are unable to validate the FRAX-derived estimates with prospective data from Ecuadorian cohorts at this time. However, a systematic review of fracture risk prediction tools highlighted that the FRAX algorithm had the largest number of independent, externally validated studies, using Western and Asian cohorts[19]. A comparison of FRAX-based guidelines using prospective cohorts has only been implemented in a few countries[27].

In conclusion, the present study demonstrates that it is possible to apply FRAX-based assessment strategies using the same principles that have been applied in guidelines elsewhere, but adapted to the epidemiology of Ecuador.

This strategy has allowed us for the first time to ascertain the proportion of the female population with a high risk of fracture and therefore eligible for treatment according to the different age-specific thresholds and an

alternative threshold for older individuals. It is hoped that the application of these thresholds will avoid unnecessary treatment of people at low risk of fracture and direct treatment to people at high risk.

Although no model can universally fit the profile and needs of all countries, in countries with low to moderate risk of fracture, and with limited resources, a hybrid model may be the most appropriate.

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

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Rev Osteoporos Metab Miner. 2022;14(2):82-87

Changes in bone mass in a child population with type 1 diabetes mellitus. Longitudinal study

DOI: http://dx.doi.org/10.4321/S1889-836X2022000200004

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Date of receipt: 30/09/2021 - Date of acceptance: 07/02/2022

Summary

Objetive: To evaluate, over a 79.2-month follow-up period, the behavior of bone mineral density (BMD) determined by Computerized Axial Densitometry (DXA), volumetric bone mineral density (BMDvol) and its relationship with anthropometric data, together with the parameters related to bone metabolism (calcium, phosphorus, alkaline phosphatase, parathormone (PTH) and vitamin D (25-OH-D3)) in a child population with Type 1 Diabetes Mellitus (DM1) without microvascular complications and a control group of reference with similar characteristics.

Material and methods: Initially, a cross-sectional study was carried out in 40 diabetic children (mean age 9.4±2.8 years) and 108 controls (9.3±1.5 years) to assess the possible differences between the two populations. 26 patients from the initial diabetic group were reassessed after 79.2 months of follow-up.

Results: It was observed that, at baseline, bone mass was similar in diabetics and controls. After follow-up, the BMD of the diabetic children was much lower than that expected in the non-diabetic child population.

Weight, height, and Body Mass Index (BMI) followed the same pattern as BMD. The values of calcium, phosphorus, alkaline phosphatase, PTH and vitamin D, although within the normal range, were lower than in the controls. Alkaline phosphatase did not increase in the pubertal period.

Conclusions: The present study demonstrates that children and adolescents with a recent diagnosis of DM1 have a normal BMD. However, over time, and especially during adolescence, they show less bone mass gain and changes in bone turnover parameters.

Key words: type 1 diabetes mellitus, childhood, bone mineral density, bone turnover, longitudinal study.

Introduction

Type 1 diabetes mellitus (DM1) has been associated with lower bone mass for more than 30 years[1,2], although existing data in children and adolescents are contradictory[3-8]. Published results on bone mass development in the adult diabetic population show a lower BMD in type 1 diabetics that persists over time and a higher risk of fractures[9-11]. However, in the pediatric population with DM1, longitudinal studies are very limited and with discrepant results. Some authors report a reduction in BMD during follow-up[6,12,13], while others do not observe long-term changes[14,15]. These discrepant results may be due to multiple variables such as the length of follow-up, which is almost always too short; the different ages and anthropometric variables, or the different pubertal stages of the diabetic population included in the studies[11-14].

Few publications longitudinally evaluate BMD in children with long-term DM1, also relating it to the different parameters of bone metabolism and remodeling and to the degree of diabetes control[11,16].

Therefore, our study aim has been to compare the BMD of children and adolescents with type 1 diabetes, with a control group with similar anthropometric characteristics, and to carry out a long-term follow-up of this population, relating the changes in bone mineral density with data anthropometric, degree of metabolic control, analytical parameters related to calcium metabolism, serum levels of parathormone and vitamin D.

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Material and methods

Study design

This study includes 2 phases. The first consisted of a cross-sectional study in which bone mass was compared between control children and type 1 diabetic children, while in the second phase an observational longitudinal study of this population was carried out, reevaluating it after a long period of time (mean: 79.2 months).

Study subjects

There were 40 diabetic children (17♂/23♀) included in the study ranged in age from 3.3 to 16.7 years at the outset of the study, with a disease duration of 4.04±2.8 years (9.4±2.8 years) and with no obvious microvascular complications. 70% of the diabetic population studied was in Tanner stage I, 10% in stage II, another 10% in stage III, 7.5% in stage IV and 2.5% in stage V of pubertal development. All of them came from the Pediatric Endocrinology clinic of the "Virgen de Macarena" University Hospital in Seville. The 109 controls (55♂/54♀) (mean age: 9.32±1.6 years) with an age range of 6.1 to 16.9 years, were included by age, sex and pubertal stage, similar to the study group.

In the second phase of the investigation, 26 of the 40 diabetic patients (13♂/13♀) initially studied (65%) were reassessed after a mean follow-up of 79.2 months, when their mean age was 15.88± 2.9 years and the mean evolution of the disease of 10.61±3.0 years (range 5-18). After this follow-up period, these patients did not show complications secondary to their underlying disease. At this point in the study, 73.1% of the patients were in Tanner stage V, 11.5% in stage IV, 3.8% in stages II and III, respectively, and 7% were in stage I of pubertal development.

The remaining 14 patients included in the initial study could not be located due to changes in their address and/or assigned health area.

The longitudinal study results were compared with a reference control population of 234 children, matched by age, sex and pubertal stage with the cases, in whom BMD was assessed in the same period of time as the diabetic population.

Bone mass

In all study participants, both those included in phase 1 and 2, areal BMD, volumetric density (vol BMD), anthropometric parameters (age, weight and height), pubertal stage, menarcheal age of girls, serum levels of calcium, phosphorus, alkaline phosphatase, PTH and 25-OH-D3 were assessed. In the diabetic population, the mean values of glycosylated hemoglobin (HbA1c) were collected (obtained based on all HbA1c determinations since the initial diagnosis), number of years of the disease, existence of complications and regimen of administered insulin, expressed in IU/Kg/day.

Weight and height were obtained using a platform scale and an Atlántida S-11 stadiometer (Año Sayol S.A. Barcelona). Body mass index was calculated as weight/height^2 (Kg/m^2).

BMD was measured by DXA (Hologic-QDR-1000) in the lumbar spine (L2-L4). BMD measurement was performed with the same densitometer in both phases of the study. The Z-score of the control population was used as a reference for bone mineral density. The coefficient of variation (CV) of DXA was 0.5% in vitro (phantom) and the CV in vivo was 1.4%.

To avoid the variable size of the vertebrae in a growing population as a confounding factor, volBMD was determined, following the formula described by Kroger et al.[17].

Analytical parameters and bone remodeling

Blood samples for the different serum determinations were taken under fasting conditions, using the same measurement techniques in both phases of the study. Biochemical parameters (calcium, phosphorus, and alkaline phosphatase levels) were determined by autoanalyzer.

The degree of metabolic control was evaluated by determining the HbA1c levels by HPLC (high performance liquid chromatography), where the mean level was obtained based on all the determinations made from diagnosis to inclusion in the study (minimum 3 determinations per patient not anymore). Good metabolic control was considered when the mean HbA1c values were less than 7%; moderate control when they ranged between 7 and 8.5% and poor metabolic control when HbA1c figures were greater than 8.5%.

Parathormone (PTH) was measured by chemiluminescence immunometry. The determination was made by photometric analysis with a 2nd generation IMMULITE DEP (Dipresa) autoanalyzer. Its normal range was considered between 15-80 pgr/ml.

Serum 25-OH-D3 was quantified by R.I.A. (Nichols Institute Diagnostics USA), after separation of the vitamin D metabolites. All the samples were collected in the same summer period to avoid bias.

All the patients' parents were informed of the purpose of the study and their consent was previously obtained. Likewise, the approval of the Ethics Committee of the Center was obtained.

Statistic analysis

Results are presented as mean ± standard deviation (SD). Statistical treatment was carried out using the statistical package "(SPSS) 22.0". To compare the means between the groups studied, Student's t test was applied to paired data and independent data when they followed a normal distribution. The Mann-Whitney U test was used with variables that did not show a normal distribution. Bone mineral density, weight, height, and BMI are expressed in absolute values. In the longitudinal study, the reference values of weight, height and BMI have been expressed as Z-score (value of BMD, weight, height and BMI of the patients-mean values of the control group/SD), to evaluate the changes that produce in time. The relationship between BMD (expressed in Z-score) and the rest of the parameters studied was calculated using the Pearson correlation coefficient in the case of those variables that followed a normal distribution; otherwise, the correlation coefficient used was Spearman's. Confounding factors were identified by multivariate analysis and, in the second part of the study, by a repeated measures test. Values of $p<0.05$ were considered levels of statistical significance.

Results

The anthropometric data and baseline biochemical parameters of the groups studied are included in table 1.

We have not observed significant differences in bone mass between DM1 and controls, neither globally, nor when comparing them by sex. There were also no significant differences in weight and height between patients

and controls, although the BMI was lower in diabetic children. 70% of the children included in this first part of the study were in Tanner stage I.

Serum calcium was significantly higher in the diabetic population. Phosphorus did not show differences between both populations. Circulating levels of 25-OH-D3, PTH, and alkaline phosphatase (AP), although within the normal range, were significantly lower in the diabetic population than in the control group (table 1).

The positive correlation between BMD and alkaline phosphatase present in the control group (r=0.198 p=0.04), is not observed in the diabetic group.

In children with DM1, serum HbA1c levels were 8.5±1.4% and the mean duration of the disease was 4.04±2.8 years. We did not find any relationship between BMD, the degree of metabolic control (HbA1c) and the time of evolution of the disease.

The anthropometric, biochemical and BMD data of the patients included in the longitudinal study (baseline and after 79.2 months) are shown in table 2.

At the end of the study, in diabetics, bone mass had increased significantly in absolute values from 0.715±0.13 gHA/cm^2 to 0.940±0.12 HA/cm^2; p=0.000), as expected in a stage of full growth. However, the BMD values (expressed in Z-score) were significantly lower than those found in the first phase of the study (0.537±1.12 Z-score vs. -0.116±1.03 Z-score; p=0.001). This implies that the bone mass gain was much lower than expected for their age and gender (figure 1).

Vol BMD showed the same behavior as areal BMD, clearly correlating with it at the L2-L4 level (r=0.835) p=0.001.

Table 1. Anthropometric data and biochemical and bone mineral density parameters of patients with diabetes mellitus-1 and controls

	Diabetics N=40 X±SD*	Controls N=10 X±SD*	P#
Age (years)	9.3±1.5	9.4±2.8	NS
Weight (kg))	33.7±11.0	35.6±10.7	NS
Size (cm)	133.7±16.3	133.6±10.0	NS
BMI** (Kg/m^2)	18.3±3.0	19.5±3.8	P=0.05
BMD** (gHA/cm^2)	0.761±0.1	0.756±0.9	NS
Z-score (SD)	0.059±0.15	0.0±0.0	NS
Calcium (mg/dl)	9.6±1.6	9.0±0.35	P=0.000
Phosphorus (mg/dl)	4.8±1.0	4.6±0.42	NS
Alkaline phosphatase (U/L)	288.0±97.3	492.5±159.4	P=0.000
PTH** (pg/ml)	24.4±12.7	30.7±13.6	P=0.01
25-OH-D** (ng/ml)	27.5±16.5	40.2±9.9	P=0.000

*X±SD: mean ± standard deviation; #: statistical significance p<0.05; **BMI: Body Mass Index; BMD: Bone Mineral Density; PTH: parathormone; 25-OH-D: vitamin D.

Table 2. Anthropometric and biochemical data of the diabetic population, baseline and after almost 7 years of follow-up

N=26	Basal X±SD*	After 79.2 months X±SD*	P#
Age (years)	9.23±3.3	15.88±2.9	0.000
Weight (Kg) (Z-score)	0.836±0.89	0.187±0.90	0.002
Size (cm) (Z-score)	0.629±0.87	-1.092±1.40	0.000
BMI** (%) (Z-score)	0.63±1.3	0.47±1.0	0.000
BMD** (gHA/cm^2)	0.715±0.13	0.940±0.12	0.000
Z-score (SD)	0.537±1.1	-0.116±1.0	0.001
HbA1c (%)	8.8±1.3	9.3±1.9	NS
DMOA** (gr/cm^3)	0.138±0.15	0.149±0.14	0.000
Calcium (mg/dl)	9.9±0.3	9.6±0.1	0.01
Alkaline phosphatase (U/L)	299.5±99.3	269.8±151.9	NS
PTH** (pg/ml)	27.3±12.4	19.8±7.7	NS
25-OH-D** (ng/ml)	27.9±18.1	40.4±17.4	0.02

*X±SD: mean ± standard deviation; #: statistical significance p<0.05; **BMI: Body Mass Index; BMD: Bone Mineral Density; DMOA: Areal Bone Mineral Density; PTH: parathormone; 25-OH-D: vitamin D.

At the beginning of the follow-up, 6 of the 26 patients presented negative BMD values (expressed in Z-score), even in three of them, the values were lower than -1SD. At the end of the study, there were 14 patients who presented a BMD below the expected values for their age and gender, doubling the number of them with -1SD. Only 4 diabetics showed an increase in bone mass consistent with the period of bone mass apposition expected for a growing adolescent population.

We did not explore the influence of pubertal stages on BMD, since most of the cases (19 of the 26) were in the last Tanner stage, and the rest of the patients were distributed in the remaining stages, being fairly homogeneous group.

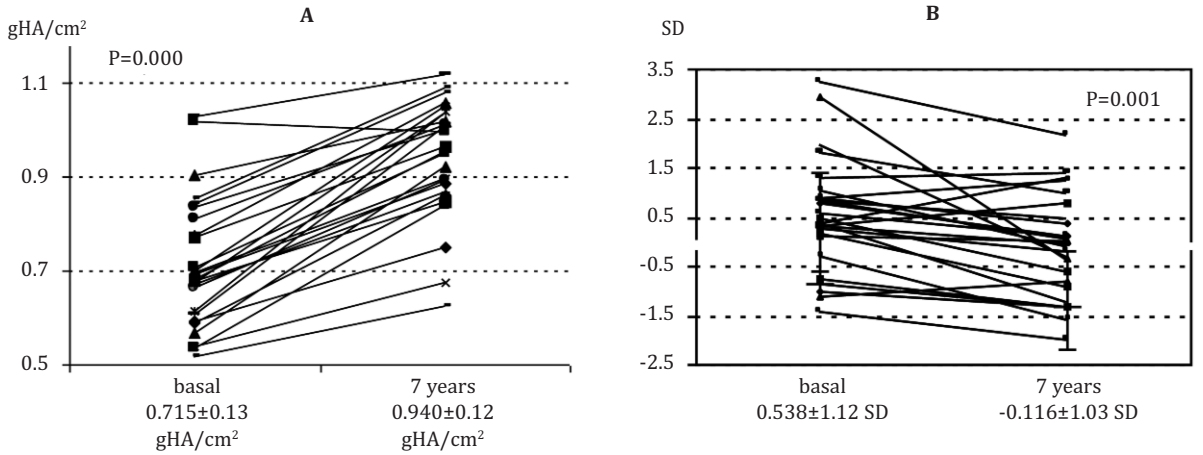
The analysis by gender showed comparable results, with a non-significant lower BMD gain in adolescents.

Mean HbA1c levels after follow-up were 9.31±1.98% with a range of 6.4-14.4%. None of our patients had good metabolic control; 12 of them had moderate control and 14 were poorly controlled. We have not observed any relationship between changes in bone mass and the degree of metabolic control or the duration of the disease.

The same behavior that bone mass showed was observed when evaluating weight, height and BMI. Although these parameters increased significantly in absolute values, the diabetic patients had BMI values expressed in Z-score that were significantly lower than those found at the beginning of the study (table 2).

In phase 2 of the investigation, calcium levels decreased and vitamin D levels were significantly higher than baseline levels in the diabetic population (table 2).

Figure 1. Changes in bone mineral density after 79.2 months of follow-up expressed in absolute values (A) and in Z-score (B)



The changes produced in BMD at the end of the study were not influenced by pubertal stage. We observed that, although the older group (>15 years) reached more negative Z values from lower values in the initial study, the lower BMD gain is similar in both groups (figure 2).

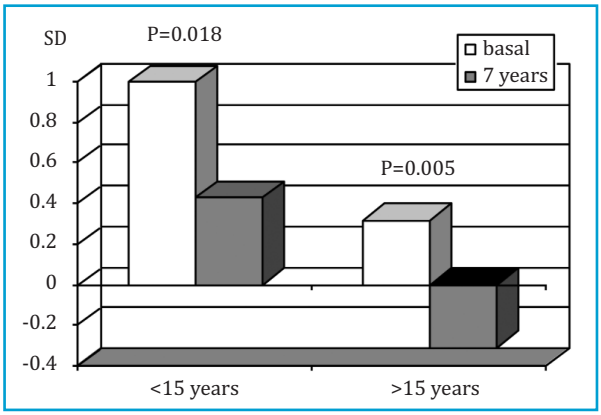
In the multivariate analysis to determine the possible influence on bone mass of different variables (weight, height, BMI, serum calcium and 25-OH-D3), we found that only BMI was independently associated with the value of the score. Z (95% CI: 0.150-0.890; p=0.009) beta coefficient: 0.535.

Discussion

In our study, the child population with DM1 and with a short duration of the disease, showed a bone mass similar to that of the healthy population. These data corroborate the findings obtained in a previous study of our group, with a type 1[18] diabetic population. After a follow-up period of almost 7 years, BMD and volBMD increased in absolute values, but bone mass gain did not reach the desirable levels for a non-diabetic population with similar characteristics (figure 3).

Although there are numerous cross-sectional publications to evaluate bone mass in children with DM1, longitudinal studies carried out in this population are very limited, and with a follow-up period that is too short. We have only found one publication, which covers a broader period[6].

Figure 2. Evolution of bone mass in type 1 diabetics, grouped by age (Z-score)



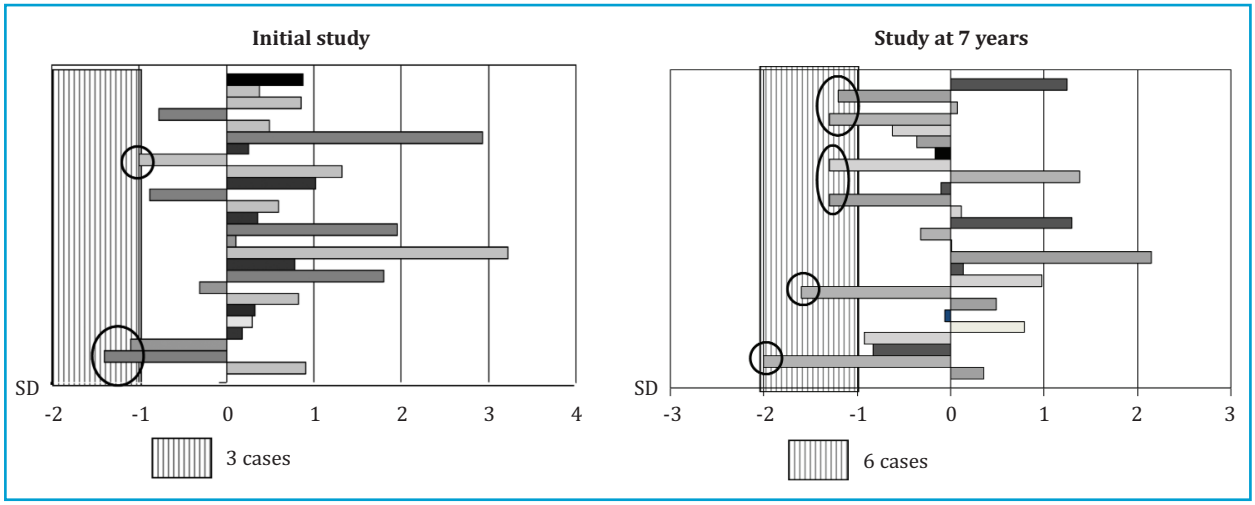
Those publications found that show no changes or these are minimal in the BMD of children with DM1, are carried out in a very short period of time (12 months)[12,14] and some start from a lower initial bone mass12. Hui et al.[15], with a somewhat longer follow-up (3 years), did not find changes in bone mass in a large population with type 1 diabetes either, but based their results on the measurement only of cortical bone in different locations of the radius, and the mean age of the patients is much higher than that of our diabetic population.

We have only found one study6 with characteristics similar to ours in temporality and study population. These authors observe a lower bone mass gain in the diabetic population than in controls. Unlike our study, they include patients with microvascular complications (5%) and the duration of DM1 was not homogeneous, with considerable variability between subjects, both at baseline and during follow-up. Despite this, their results are very similar to ours.

The discrepancy in bone mass results in the child population with DM1 could be explained by multiple factors: different bone mass measurement methods, type of bone measured (trabecular or cortical), age and number of patients included, or different stages puberty of the children studied[3,7,15,19]. To save the influence of changes in BMD induced by sex hormones, we selected a fairly homogeneous initial group, with 70% of cases in Tanner stage I. Like most authors, we have not found any relationship between bone mineral density and the degree of metabolic control or the time of evolution of the disease[4,13,14,15]. In our case, none of our diabetics had good metabolic control, which prevented us from making a comparison in this regard.

Our type 1 diabetic child population gains less weight, less height and their BMI is lower than expected for a healthy population of similar age and gender. BMI correlated with BMD. Studies that find a lower height and lower weight in prepubertal type 1 diabetic children with poor metabolic control relate it to a lower secretion of IGF-1 secondary to insulin deficiency[20-22]. In our case, almost all the patients had poor metabolic control and the onset of the disease had manifested before puberty except in one case, which could explain these metabolic alterations, and the lower bone mass gain.

Figure 3. Number of patients with values less than -1 SD (expressed in Z-score) in the initial study and after a 7-year follow-up (the position of the bars correspond to the same patient)



There are few works that relate the biochemical parameters with the changes experienced in the BMD of children with DM1. Most studies are cross-sectional and show disparate results. Of the few follow-up studies that measure bone mass in diabetic children, few include biochemical parameters[12,14]. Although our patients had serum levels of calcium, phosphorus, alkaline phosphatase, PTH, and vitamin D within the normal range, these were lower than in the control population. In cross-sectional studies of adolescent or adult populations, the results have been similar[4,23-25]. It is suggested that, possibly, this altered metabolic control is conditioned by low insulin levels, giving rise to abnormalities in calcium metabolism and, therefore, to low bone formation[23,24,26-28]. The hypotheses about decreased PTH levels are based on the insulinopenia present in type 1 diabetics or on a decrease in the activity of the enzyme 1-alpha-hydroxylase-renal, and could be related to the lower weight gain they present type 1 diabetics[28,29]. As with other authors' observations, we did not find any relationship between these biochemical parameters and bone mass[4,24,25,30,31].

In our results, the serum alkaline phosphatase values stand out, which, although within the normal range, were significantly lower than those of the controls in phase 1 of the study. After almost 7 years, these values did not increase as occurs in the non-diabetic adolescent population and were negatively and significantly related to bone mass in phase 2. This could be explained by the lower growth and acquisition of bone mass that we detected in patients with DM1. This aspect has not been evaluated in longitudinal studies of children with DM1. Cross-sectional studies do not find these differences[4,32].

Although our study is of great interest due to the homogeneity of the samples and the long follow-up, it has limitations. First, the number of cases studied may be insufficient to draw definitive conclusions. Furthermore, serum levels of Insulin-like Growth Factor-1 (IG-F1), sex hormones and insulin have not been determined, which would undoubtedly help us improve our understanding of the pathophysiology of the disorder.

Although it would have been desirable to longitudinally evaluate the control subjects' BMD, we have compared the data of the diabetic population studied almost seven years later, with a second healthy control group, with adequate bone apposition and similar anthropometric characteristics, obtained from a cross-sectional analysis. We believe this does not detract from the validity of our study, since the results clearly show the lower bone mass gain in type 1 diabetic children even without the presence of microvascular complications, as in other publications carried out with the same methodology.

In *conclusion*, the present study shows that children and adolescents recently diagnosed with DM1 have normal BMD. However, with the passage of time and, above all, in the period of adolescence, they show less bone mass gain.

The changes observed in the parameters of bone turnover after a long follow-up period could be interpreted as a consequence of insulin deficiency that causes poor metabolic control. The lower weight and height obtained at the end of the study could justify, together with these bone metabolic alterations, the lower bone mass gain acquired by diabetic patients. All these findings will lead to a lower peak bone mass and, surely, to a higher risk of developing osteoporosis and fragility fractures in adulthood.

Conflict of interests: MJMG. Scientific advice and funding for attendance at scientific congresses from AMGEN and UCB laboratories.

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Rev Osteoporos Metab Miner. 2022;14(2):88-92

Effect of treatment with denosumab for 24 months in individuals with recent spinal cord injury with osteoporosis

DOI: http://dx.doi.org/10.4321/S1889-836X2022000200005

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Date of receipt: 14/03/2022 - Date of acceptance: 11/05/2022

Summary

Introduction: Osteoporosis development is a frequent complication associated with spinal cord injury (SCI), especially at the sublesional level. However, at present, data on its treatment are scarce.
Aim: To analyze bone mineral density (BMD) and bone turnover markers (BTM) after 2-year treatment with denosumab in individuals with SCI-related osteoporosis.
Methods: Prospective study including patients with recent SCI and related osteoporosis treated with denosumab for 24 months. In all patients, BTMs (bone ALP, sCTX and PINP), 25-OH-vitamin D levels and lumbar and femoral BMD were assessed at baseline and at 12 and 24 months.
Results: 13 patients (aged 39±15 years) with recent SCI (mean duration of 15 months) and osteoporosis treated with denosumab for 24 months were included. Patients showed a significant increase in BMD at lumbar spine and proximal femur after 12 months of treatment with denosumab, with a further increase in BMD at 24 months of follow-up, reaching an increase of 9.1% in lumbar spine, 4.4% in femoral neck and 5.3% total femur, respectively. BTM significantly decrease at 12 months and remained decreased at 24 months of follow-up. No skeletal fractures or treatment-related adverse events were observed during follow-up.
Conclusions: Treatment with denosumab during 24 months increases lumbar and femoral BMD and decreases BTMs in patients with recent SCI. Denosumab may be a promising therapeutic option in SCI-related osteoporosis.

Key words: denosumab, osteoporosis, spinal cord injury, bone mineral density, bone turnover markers.

Introduction

After a spinal cord injury (SCI) there is a marked loss of bone mass and an increase in remodeling that leads to the development of osteoporosis and skeletal fractures, especially below the level of the injury[1-3]. Thus, more than 50% of patients with complete SCI develop densitometric osteoporosis one year after SCI[1], which can reach 81% of patients after more than 5 years of SCI[4]. However, despite the high incidence of osteoporosis and fractures, the therapeutic approach to these patients is clearly deficient, since less than 10-20% of them receive anti-osteoporotic treatment[2,5].

There are few studies that analyze the effect of anti-osteoporotic treatment on osteoporosis associated with SCI. In this sense, treatment with oral or intravenous bisphosphonates, especially zoledronate, has been shown to reduce the loss of bone mineral density (BMD) in this process. However, in patients with recent SCI, in whom there is a rapid and marked loss of BMD associated with an increase in bone turnover, its efficacy is lower, especially at the infra-lesional level, in the lower limbs[6-9], where most fragility fractures occur in these patients[2]. Along the same lines, teriparatide, a bone-forming treatment, has also not shown efficacy in preventing bone

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loss in this process[10]. All this indicates the need to improve the therapeutic approach in these patients, not only at the advanced stages of the disease, but also early after SCI, when the magnitude of bone loss is greater, thus preventing associated long-term complications.

Denosumab, a monoclonal antibody directed against RANK-ligand, is an essential mediator for osteoclast differentiation and survival, with a marked antiresorptive effect and demonstrated effectivity in the treatment of postmenopausal and male osteoporosis[11]. It offers a remarkably positive effect on cortical bone, such as the proximal femur or distal forearm[11]. Therefore, the use of denosumab could be especially indicated in treating patients with SCI and osteoporosis. In fact, an increased expression of RANKL was observed in an animal model of mice with SCI[12], suggesting a potential therapeutic role for denosumab in this clinical situation. Similarly, in a recent exploratory study that included a limited number of patients with SCI, a preventive effect of denosumab on bone loss a few months after SCI was observed[13]. We previously reported a positive effect of this type of treatment in patients with SCI and osteoporosis during a 12-month follow-up period[14].

This study reports our experience in patients with recent complete motor SCI treated with denosumab over 24 months.

Patients and methods

Study design and patient selection

This study is part of a prospective observational study with the main objective of analyzing the effect of recent SCI (<6 months) on bone mass loss and bone metabolism in these patients[1]. The patients were consecutively recruited at the Guttmann Neurohabilitation Institute, and subsequently referred to the Metabolic Bone Pathology Unit of the Rheumatology Service of the Hospital Clínic de Barcelona. Antiosteoporotic treatment was indicated in those patients who presented densitometric OP during follow-up. In patients with 25-OH-vitamin D deficiency ([25-OHD] <20 ng/ml), vitamin D supplements were indicated. The study was approved by the ethics committee of the Hospital Clínic de Barcelona and the Guttmann Neurorehabilitation Institute. All patients signed the informed consent prior to their inclusion.

In this study, we present data on the effect of anti-osteoporotic treatment with denosumab on BMD evolution of bone turnover markers (BTM) in individuals with SCI who developed osteoporosis during follow-up and completed 24 months of treatment with denosumab, with 13 patients included.

Methods

All patients underwent a clinical and analytical assessment with BTM quantification and bone densitometry at baseline and at 12 and 24 months of follow-up.

Osteoporosis risk factors, body mass index (BMI), and injury characteristics were collected, including the level of SCI (tetraplegia/paraplegia), the presence of spasticity, and the severity of SCI according to the scale of AIS[15] that classifies according to motor and sensory involvement in 5 categories: A: complete motor and sensory SCI; B: complete motor and partial sensory SCI; C and D: partial motor and sensory; E: no motor or sensory lesion. The incidence of skeletal fractures and potential adverse effects during follow-up were also collected.

Analytical determinations

Analytical determinations included: creatinine, calcium and phosphate by automated methods. The values of 25-OHD (Liason DiaSorin) and the following BRMs were quantified: bone alkaline phosphatase (bone FA by IDS, Vitro), type I procollagen amino-terminal propeptide (PINP by Cobas e411, Roche) and type I collagen carboxyterminal telopeptide. I (CTX by Cobas e411 automated method, Roche).

Bone mineral density

Lumbar spine and proximal femur BMD (femoral neck and total femur) were quantified by dual X-ray absorptiometry (DXA; Lunar Prodigy, Radiation Corporation Madison, WI) at baseline, and at 12- and 24-month follow-up. The densitometric categories were defined according to WHO criteria (normal BMD, osteopenia and osteoporosis)[16].

Statistic analysis

The results have been expressed as the mean ± standard deviation of the mean (SD). The differences between means of the continuous variables were analyzed using Student's t-test and the differences between proportions using the Chi-square. To compare paired variables (baseline and 12 months; 12 months and 24 months; baseline and 24 months) the Wilcoxon non-parametric test was used. To assess the association between analytical and densitometric variables, the Pearson correlation coefficient was used. The value $p<0.05$ was considered statistically significant.

Results

The clinical characteristics of the individuals included in the study are shown in table 1.

In all, 13 men were included, with a mean age of 39±15 years at 15±4 months after having suffered SCI. All patients had severe SCI (ASIA A or B) and 61% had tetraplegia. Most of them had spastic-type SCI (85%) and all of them required a wheelchair to get around. The main cause of SCI was traffic accident (85%). One patient presented SCI attributed to precipitation and another due to a sports accident. All the patients included in the study had developed osteoporosis during the initial follow-up period (prior to starting anti-osteoporotic treatment with denosumab).

At 12 months from the start of treatment with denosumab, a significant increase in BMD was observed in all locations analyzed: lumbar spine (+7.47±3.67%, p=0.001) and femoral neck (+3.03±3.73, p=0.019) (table 2 and figure 1). Likewise, at 12 months, a significant decrease was observed in all the ROM: bone FA (-41±22%, p=0.003); PINP (-53±26%, p=0.001) and CTX (-59±29%, p=0.002) (figure 2).

At 24 months of treatment, an additional increase in BMD was observed in all locations. Thus, the patients achieved a total increase in BMD at 24 months of +9.1±4.4% in the lumbar spine (p=0.002); +4.4±5.1% in the neck of the femur (p=0.033) and +5.3±5.7% in the total femur (p=0.011) (table 2 and figure 1). The BTMs persisted decreased at 24 months with an overall decrease in bone FA (-38±27%, p=0.003); PINP (-43±27%, p=0.001) and CTX (-42±35%, p=0.005) (table 2 and figure 2).

BMD evolution was not related to changes in BTM or 25-OHD values. No patient presented skeletal fragility fractures during follow-up or adverse effects associated with treatment.

Discussion

The results of this study confirm the efficacy of denosumab in the treatment of osteoporosis associated with recent onset SCI, not only in the prevention of bone loss but also in the sustained increase in BMD after 24 months of treatment. Thus, treatment with denosumab for 24 months was associated with a progressive and significant increase in bone mass in all skeletal locations, both in the lumbar spine and at the sub-lesional level, in the proximal femur, and with a sustained decrease in BTM during the 24-month treatment period.

The results presented indicate that treatment with denosumab in patients with osteoporosis associated with SCI not only prevents the loss of bone mass, but even partially reverses this loss, reporting an increase of +7.47% in the lumbar spine and +3% in femoral neck at 12 months of treatment. In addition, and as expected, the patients achieved a greater increase in bone mass after the second year of treatment with denosumab, up to +9% in the lumbar spine and +5% in the proximal femur. While untreated patients, according to the literature, present sustained BMD losses between 2% and 21%[1,17-20], depending on the location evaluated (spine and/or proximal or distal femur), and the time of evolution of SCI, observing the greatest losses of BMD during the first 1-2 years after its establishment[19-20].

Although this is an observational study that includes a small number of patients, it is important to point out that denosumab produced an increase in BMD, not only in the lumbar spine, but also at the sub-lesional level, in the neck of the femur and in the total femur, and that was 9.1% in the lumbar spine, 4.4% in the neck of the femur and 5.3% in the total femur after two years of treatment. To date, this is the only anti-osteoporotic treatment that has been associated with a BMD increase in patients with OP associated with a recent SCI. Our patients had complete motor SCI with a mean onset time of 15 months, which usually coincides with the period of greatest bone loss[3,19-20], in which, with the exception of denosumab[13]. There does not seem to be an effective anti-osteoporotic treatment, particularly to prevent infralesional loss in lower limbs. In this sense, treatment with antiresorptive drugs, such as oral and/or intravenous bisphosphonates (including alendronate, pamidronate or zoledronate), or bone formers, such as teriparatide, have only been shown to attenuate the loss of bone mass in the lower limbs after a recent SCI[6-10,21-22]. However, in patients with long-standing SCI, in whom the magnitude of bone loss and bone turnover has decreased, bisphosphonates seem to have a preventive effect[6,7]. Although, the need to carry out new studies that include a greater number of patients with longer follow-up time to evaluate the treatment of these patients has been indicated[23].

Likewise, treatment with denosumab was associated with a decrease in the values of all the BTMs analyzed in this study (bone FA, PINP and CTX), with a decrease of the order of ~40% after 24 months of treatment, a finding that we have observed in patients with SCI with a similar evolution time who did not undergo this treatment, in whom an increase in BTM persists[24]. This decrease was similar in magnitude to that reported in the treatment of postmenopausal osteoporosis and in men with this type of therapy[11,25].

On the other hand, although this is an observational study that includes a small number of patients, no side effects related to denosumab treatment or the development of new skeletal fractures were observed during the 24-month follow-up.

Table 1. Clinical, analytical and densitometric characteristics of patients with SCI at baseline

	LM treated with denosumab (n=13)
Clinical features	
Age (years)	39±15 (19–65)
Sex/male (n, %)	13 (100)
BMI (Kg/m^2)	23±4 (16–32)
Calcium intake by diet (mg/day)	550±387
Daily alcohol consumption (n, %)	1 (8)
Active smoking (n, %)	1 (8)
Characteristics of the LM	
LM evolution time (months)	15±4 (8–21)
Complete motor involvement: ASIA A or B (%)	100
Wheelchair use (%)	100
Paraplegia/tetraplegia (%)	39/61
Spasticity (%)	85
Bone metabolism parameters	
Calcium (mg/dl)	9.8±0.34
Phosphate (mg/dl)	3.7±0.34
25-OHD (ng/ml)	30±28
Densitometric data	
Lumbar BMD (g/cm^2)	1.177±0.128
Lumbar T-Scale (SD)	-0.58±1.09
Lumbar Z scale (SD)	-0.43±1.14
BMD neck of femur g/cm^2)	0.759±0.084
Femoral neck T scale (SD)	-2.39±0.64
Femoral neck Z scale (SD)	-1.86±0.76
Total femur BMD (g/cm^2)	0.727±0.067
Total femur T scale (DE)	-2.78±0.52
Total Femur Z Scale (DE)	-2.48±0.58

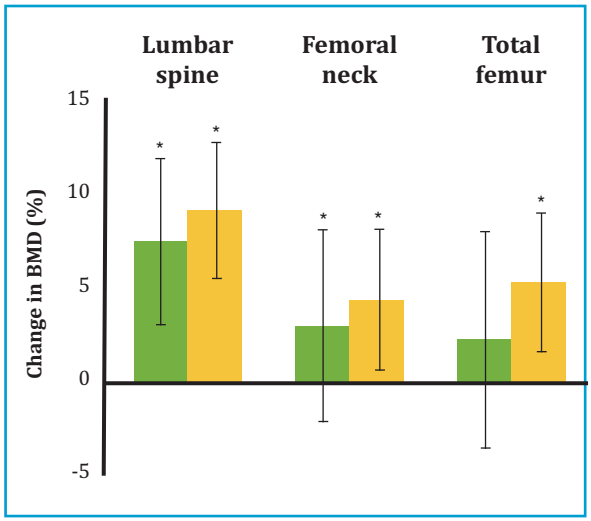
Results expressed as mean ± SD, n and %.
LM: spinal cord injury; BMI: Body Mass Index; 25-OHD: 25-OH-vitamin D; SD: standard deviation.

Table 2. BMD development and bone remodeling markers at 12 and 24 months of treatment with denosumab

	Basal	12 months	24 months
Densitometric data (BMD)			
Lumbar (g/cm^2)	1.177±0.128	1.262±0.113*	1.282±1.124*
Femur neck (g/cm^2)	0.759±0,084	0.782±0.091*	0.793±0.103*
Total femur (g/cm^2)	0.727±0.067	0.743±0.060	0.766±0.082*†
Bone remodeling markers			
PINP (ng/mL)	70±29	29±13*	35±12*
Bone AP (ng/mL)	16.6±5.2	8.8±2.6 *	9.3±2.9*
CTX (ng/mL)	0.713±0.439	0.210±0.101*	0.315±0.187*

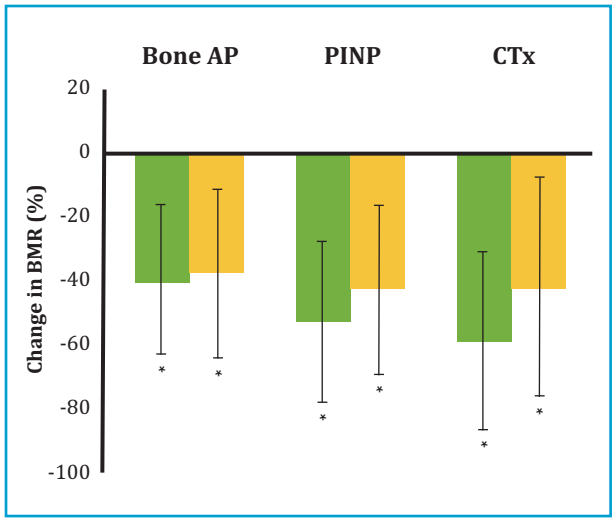
Results expressed as mean ± SD.
* p<0.05 compared to baseline values.
† p<0.05 compared to values at 12 months.
BMD: bone mineral density; P1NP: type I procollagen amino-terminal propeptide; Bone AP: bone alkaline phosphatase; CTX: carboxy-terminal telopeptide of type I collagen.

Figure 1. Percentage change in BMD (± standard deviation) in the lumbar spine, total femur, and femoral neck at 12 (green bars) and 24 (orange bars) months after starting treatment with denosumab



* p<0.05 compared to baseline values.

Figure 2. Percentage change in BMR (± standard deviation) at 12 (green bars) and 24 months (orange bars) after starting denosumab treatment



* p<0.05 compared to baseline values.

There are few studies that assess the effect of anti-osteoporotic treatment in the medium term in individuals with SCI. Most studies published to date include only 6-24 months of treatment with teriparatide, bisphosphonates, or denosumab[6-10,13,14,18,21,22].

This is the first observational study that assesses the effect of anti-resorptive treatment with denosumab for 2 years in individuals with OP associated with SCI.

Although the small number of patients and the absence of a control group constitute limitations of the study, it is important to highlight that it is a homogeneous cohort of patients, which includes men with recently established complete traumatic SCI with six-monthly follow-up, and in the that all patients experienced a marked and rapid loss of infralesional BMD after SCI[1]. Therefore, despite the characteristics of the study, we consider that these results provide useful information in the management of osteoporosis associated with this entity.

In conclusion, patients with OP associated with recent onset SCI treated with denosumab for 24 months show a significant increase in BMD at the lumbar and femoral levels. Therefore, denosumab could be a promising therapeutic option in this clinical situation. Studies that include a larger number of patients and with a longer follow-up time are needed to analyze the long-term effect of this treatment on this condition.

Acknowledgments: Study funded by Fundació La Marató de TV3.

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

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Description of the patients treated at the Fracture and Fall Prevention Unit in the context of a Fracture Liaison Service. FLS Anoia

DOI: http://dx.doi.org/10.4321/S1889-836X2022000200006

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Date of receipt: 8/12/2021 - Date of acceptance: 20/06/2022

Summary

Objective: The aim of this study is to present the performance, treatment and functional results obtained in a Fracture and Fall Prevention Unit.

Material and methods: Descriptive prospective study of patients with previous osteoporotic fracture, treated between April 25, 2016 and November 20, 2017.

Results: We analyzed 43 patients with a mean age of 80.2 years (SD±5.19), 81.40% women (n=35). Number of fractures 61,28% hip (n=17), 25% vertebral (n=15) and 21% distal radius (n=13). At discharge, all the assessment scales used improved, highlighting the results of the SPPB (39.80%), TUG (30.66%) and Tinetti (21.60%).

Conclusions: The profile patient treated corresponds to an 80.2-year-old woman, with a hip fracture, Tinetti 22:09, Daniels in extremities of 3.95, 4:05, 3.81, 3.91, SPPB of 6.63, TUG of 17.81 and FIM of 87.19 points. An improved score in all the assessed scales is reported.

Key words: Fall prevention unit, elderly, fragility fracture, Fracture Liaison Service.

Introduction

Worldwide, 1 in 3 women and 1 in 5 men will experience a fragility fracture in their lifetime. Every 3 seconds there is 1 fragility fracture in the world. The most frequent fractures associated with osteoporosis are located in the hip, spine and wrist[1,2].

Hip fracture has become an international barometer of osteoporosis, associated with low bone mineral density, high health care costs, and greater disability than other types of osteoporotic fracture[3]. Only 30% of people with a hip fracture regain their pre-fracture level of physical function, and many are left with reduced mobility, loss of functional independence, and requiring long-term care. For this reason, among other reasons, the International Osteoporosis Foundation (IOF) has developed the Capture the Fracture program, aimed at reducing secondary and posterior fractures by facilitating the implementation of Fracture Liaison Services (FLS)[1,2].

The IOF Best Practice Framework (BPF) is an internationally recognized clinical guideline for the secondary prevention of osteoporotic fractures. Structured in a series of 13 standards, the BPF addresses key elements for the success of the FLS and also includes suitability objectives, thereby stimulating excellence. Specifically, in standard number 7, fall prevention is mentioned as one of the key elements[1,2]. This led us to found a Fall Prevention Unit which we named the School of Secondary Prevention of Fractures and Falls (EPFiC, based on the Spanish title) of the Sant Josep Health Foundation (FSSJ) within the framework of the FLS Anoia.

When we focus on frailty models, such as Fried's or Watson's, many of the risk factors associated with falls are included, such as: muscle weakness, weight loss, balance disturbances, decreased gait speed, fatigue, low level of physical activity and cognitive impairment[5].

Frailty, expressed as vulnerability to adverse events, explains loss of functional capacity, falls, disability, and dependency. Between 25-28% of 80-year-olds are frail, and there is a direct relationship between frailty and falls, these being the leading cause of mortality in the el-

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derly[6]. In addition, falls generate fear of falling and this reduces physical functioning, social activities, loss of confidence, dependency, social isolation and decreased quality of life[4]. We therefore refer to the deterioration of physical performance and falls are among the most robust factors that tend to activate the negative spiral of frailty[5].

The only interventions that have been shown to be effective in preventing, and even reversing, the state of frailty in elderly patients are physical exercise, comprehensive geriatric assessment and management of the main geriatric syndromes, ahead of nutritional interventions or the use of certain drugs[7].

Having a good state of health and functionality are predictors of residing at home and maintaining functionality prior to a year after a hip fracture, while the worst state of health and functionality are predictors of mortality[8-10].

It is worth noting, therefore, the importance of the implementation of Fall Prevention Units, such as the School for the Prevention of Fractures and Falls (EPFiC) of the FSSJ, which began its activity in April 2016 within the framework of the FLS Anoia, in which They can provide a reduction in the risk of falls between 30% and 50%. It is reported that 50% of falls are due to multiple factors. The most prevalent associated factors are orthostatic hypotension, chronic arthropathy pain and vestibular syndrome[11].

Carrying out preventive actions to keep our elderly population out of risk and maintain a good level of functionality are essential EPFiC objectives. One of our maxims as health professionals should be to empower our society to guarantee active aging.

Unlike the proposed functional plan of the Fall Prevention Units of the Spanish Society of Geriatrics and Gerontology[12], our EPFiC's target population encompasses those patients with a previous fracture, since it is this group that benefits most by reducing the risk of new fractures when starting an anti-osteoporotic pharmacological treatment[2].

Here we describe the School of Secondary Prevention of Fractures and Falls (EPFiC) care protocol and show the functional results obtained in the first 19 months after its implementation.

Material and methods

Description of the EPFiC care protocol

Patients with fractures due to bone fragility are recruited at the Social Health Center of the FSSJ, by telephone, after receiving the request for assessment through 3 recruitment routes: from 1. Outpatient Consultations of the Hospital of Igualada: a) Geriatrics (Consultation for fractures due to bone fragility), b) Rheumatology and c) Physical Medicine; 2. Primary Care and 3. Socio-Health Care. The inclusion and exclusion criteria agreed upon in the FLS Anoia are followed and are shown in figure 1.

They are scheduled for initial functional assessment of occupational therapy and physiotherapy, with nursing supervision and support from the FFSJ rehabilitation day hospital. In this functional assessment, our staff recorded Tinetti and Daniels balance scale values for muscle strength, the Timed Up and Go (TUG) for the risk of falls, the Short Physical Performance Battery (SPPB) for frailty and Functional Independence Measure (FIM) for functional independence.

After this first assessment, the patient will carry out 24 group sessions, with a maximum of 8 people, 3 days a week on alternate days and lasting 1.45 hours. The main therapeutic components are balance re-education, strength retraining, active mobility, proprioception, vestibular re-education and re-education of the motor sequence to get up after a fall, as well as ADLs and IADLs. This therapeutic prescription schedule is coupled with exercise recommendations to improve balance and strength explained in the PreFIT Clinical Trial protocol[13,14] and in the systematic review by Sherrington C, et al.[15], as essential elements in exercise programs to prevents falls.

In addition, the patient receives an informative and educational class on nutrition and healthy habits by the dietician-nutritionist of the FSSJ for 1.5 hours, having completed the 24 group sessions. Finally, all the functional assessment scales are reassessed before discharge, and they respond to a satisfaction questionnaire.

Study design and participants

This is a prospective descriptive study of patients treated at the EPFiC in the period between April 25, 2016 and November 20, 2017.

Variables

For the analysis of the data obtained, pre-post intervention, socio-demographic variables have been collected: age, sex and type of fracture; Functional assessment variables: Tinetti scale, Daniels (right (R) and left (L) of upper limbs (UL) and lower extremities (LE)), Timed Up and Go (TUG), Short Physical Performance Battery (SPPB) and the Functional Independence Measure (FIM).

The data obtained from the satisfaction questionnaire is obtained through an unvalidated questionnaire for internal use.

This study has been approved by the Hospital de Bellvitge Ethics Committee.(PR222/15).

Statistics

In the description of the cohort, percentages and frequencies have been used for qualitative variables and medians and standard deviations for quantitative variables. To study the relationship between categorical variables, the Chi square test was used, with the correlation of Fisher's exact test for the comparison of proportions, depending on the frequencies. P-values less than or equal to 0.05 were considered statistically significant. The statistical program SPSS version 19.0 (IBM Corporation, Chicago Illinois) was used.

Results

During the study period, 45 patients were treated, 2 of whom did not complete the study, leaving a total sample of 43 patients with a mean age of 80.2 years (SD±5.19), 81.40% being women (n=35).

Number of fractures 61, of which 28% were of the hip (n=17), 25% vertebral (n=15), 21% Colles-Distal radius (n=13), 8% humerus (n=5), 5% pelvis (n=3), 5% ribs (n=3), 2% femur (n=1) and 6% other fractures (n=4).

At the time of discharge, an improvement is shown in all the assessment scales used, highlighting the improvement in the SPPB of 39.80%, of the TUG in 30.66% and in the Tinetti balance scale of 21.60% (table 1).

The satisfaction surveys collected were 36 of the 43 patients recruited, representing 83.7% participation. Of these, the average satisfaction score of the EPFiC is 9.7 points out of a maximum of 10. The 7 patients for whom there is no record of the survey was due to the fact that they did not submit it at the time of discharge.

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Discussion

In terms of methodology, our study coincides with the Clinical Trial Prefit[14] in the recruitment of patients who are in the community and who are older than 70 years.

The functional recovery obtained reflected in the improvement in the score of the scales used, especially the Tinetti scale with 21.60%, the SPPB with 39.60% and the TUG with 30.66%, cannot be correlated with a decrease in the number of falls, nor in the reduction in the number of fractures due to the design of our descriptive study. To a certain extent, the score improvement of these 3 scales could lead us to believe that the risk of falls will be reduced. This is implied by the very definition of each of the three scales in which, the better the result, the lower the risk of falls. As pointed out in the systematic review by Sherrington et al.[15], with a high level of evidence, exercise programs that include balance, functional and resistance exercises reduce the rate of falls and the number of people who experience falls, in people older people living in the community. Zhao et al.[16] also concluded that exercise had a beneficial effect in reducing fall-related fractures and reduces risk factors for fall-related fractures in older people. Hopewell et al.[17] conclude their meta-analysis by saying that, of all the multi-factor interventions, exercise prescription can reduce the rate of falls and slightly reduce the risk of one or more falls and recurrent falls in older people throughout the community.

Most of the people we have assessed with fractures due to bone fragility are women, 81.40% of the sample. The results by gender expressed by Roca F et al.[11] were also women who predominated, but in reference to falls, without being able to confirm if they were also the ones who had a higher incidence of fractures. In any case, knowing that a TUG greater than 15 seconds correlates with the risk of falling and if we look at the average TUG on admission, we can mention that there is a risk of falls and possible fractures that is reduced at the time of discharge as as reflected by the reduction of 5.46 seconds of the TUG.

In our study, the most prevalent fractures were hip in 28%, vertebra in 25% and distal radius in 21%. Currently we have not found studies of fall prevention units that provide data that allow us to compare in this regard. We have already commented recently that the great challenge of the 21st century should be the creation of multiprofessional osteoporotic fracture units in an effort to reduce the incidence of major fractures due to bone fragility (vertebra, pelvis, hip and humerus) and especially hip fractures[18].

Thus, we believe that we must redirect our efforts towards post-fracture secondary prevention, in its double version of treating osteoporosis and falls, in those people who have already had a fracture due to bone fragility.

In contrast to the proposed functional plan of a Unit for the Falls Prevention and Osteoporotic Fractures of the Spanish Society of Geriatrics and Gerontology[12] who recommend working with the elderly person who was at risk of falling or who had already fallen as a result of an osteoporotic fracture or not, our study, we focus on working with people who, although they may be at risk of falling, or have suffered previous falls, must all have a history of fracture due to bone fragility. We have considered this modification, following the recommendations of the IOF Capture the Fracture program, in which it is this population group, with a previous osteoporotic fracture, who benefits most from pharmacological intervention. Along these lines, we believe that it is this population that could benefit most from fracture and fall prevention units, bearing in mind that studies with a robust design and methodology are required to demonstrate this.

As a multidisciplinary and multilevel group, within the framework of the FLS, our aim was to implement a fracture and fall prevention unit in the context of secondary prevention in osteoporotic fractures or due to bone fragility. We are aware of the difficulties involved in organizing referral circuits and recruiting patients, given FLS Anoia's different health institutions.

Last but not least, the participants' degree of satisfaction is noteworthy, with an average score of 9.7 points out of 10. This was one of the crucial aspects for adherence during the intervention.

Figure 1. EPFiC admission/non-admission criteria for the FSSJ

Criteria for admission to the EPFiC:
- Age >69 years
- Recent previous fracture (<1 year)
- Old previous fracture and risk of falling TUG*** >15 seconds
- Risk of fall SPPB**** <7-9

Criteria for not entering the EPFiC:
- Age <70 years
- Life expectancy <12 months
- GDS-FAST* >4
- Barthel index <50
- FAC**<4

*GDS-FAST: Geriatric Dementia Scale
**FAC: Functional Ambulation Classification
***TUG: Time Up and Go
****SPPB: Short Physical Performance Battery.

Table 1. Pre- and post-intervention functional results

	Admission	Discharge	Discharge-Admission	% Improvement	p=
Tinetti	22.09	26.86	4.77	21.60	0.001
Daniels EII	3.95	4.77	0.82	20.76	0.001
Daniels EID	4.05	4.79	0.74	18.30	0.001
Daniels ESI	3.81	4.63	0.82	21.52	0.001
Daniels ESD	3.91	4.72	0.81	20.72	0.001
SPPB	6.63	9.07	2.44	39.80	0.001
TUG	17.81	12.35	-5.46	30.66	0.001
FIM	87.19	96.6	9.41	10.79	0.001

Based on our experience, we would encourage EPFiC implementation in the public health system, as well as city council strategic community health plans to guarantee adherence to therapeutic physical activity that the EPFiC has already begun. Without a doubt, this needs continuity in the community.

Limitations

As this is a descriptive study, we cannot correlate the findings of functional improvement with a decrease, or not, in falls or new fractures in this target population. Furthermore, the satisfaction questionnaire is for internal use and not validated. However, these limitations are elements for improvement in future research studies already under way.

Conclusions

Based on our findings, the profile of the post-fracture patient due to bone fragility treated at the EPFiC of the San José Health Foundation (FSSJ) in Igualada, is an 80.2-year-old woman with a hip fracture, Tinetti 22.09, Daniels in LLL, RLL, LUL and RUL of 3.95, 4:05, 3.81, 3.91 respectively, SPPB of 6.63, TUG of 17.81 and FIM of 87.19 points.

At the time of discharge, after the 24-session group treatment, a statistically significant improvement was observed in the scores of all the assessed scales. This would correlate with a reduced risk of falling. However, we do not know if this correlates with a reduction in the number of falls and, specifically, with a reduction in the number of new fractures due to bone fragility. Future studies with a very robust methodology are required.

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

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