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Risk of major osteoporotic or hip fracture in patients with cerebrovascular accident in the acute phase. Multicentre prospective study

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Summary

Objetives: Hemiplegic patients are considered to be a population at risk of suffering osteoporotic fractures. The aim of this work is to understand the absolute risk of fragility fracture in patients with cerebrovascular accident (CVA) and the osteometabolic state of patients with ictus in the acute phase, as well as confirming if there are baseline differences compared to a control group without cerebrovascular pathology.

Patients and method: Multicentre prospective study carried out in five Spanish hospitals. Two groups were established: a) patients with ictus of less than three months development, and b) a control group from a population without cerebrovascular disease. History of fragility fractures, number of falls in the previous year, bone mineral density (BMD) in the hip, FRAX® index, determinations of biochemistry and bone markers - calcium, phosphorus, alkaline phosphatase, vitamin D, parathormone (PTH), and carboxy-terminal telopeptide of collagen type I (CTX) - were analysed.

Results: A total of 82 patients were studied: 50 patients with CVA and 32 controls. 12% of those patients with CVA had an increased risk of suffering a hip fracture, and 8% an increased risk of a major osteoporotic fracture. In the control group the risk was greater. The hemiplegic patients had BMD in the hip lower than those in the control group, although the differences in both variables were not statistically significant.

The levels of CTX were higher in patients with CVA, this being the sole determination which showed a statistical difference between the two groups studied.

Conclusions: The patients with CVA had values of markers for bone resorption (CTX) significantly higher and a BMD in the hip lower than those in the control group.

Key words: *cerebrovascular accident, BMD, fragility fracture.*

Introduction

As is universally accepted, the significance of osteoporosis is rooted in the risk of it provoking fractures. Specifically, it is hip fractures which have greatest significance given their functional and economic repercussions and their impact on mortality rate. Hip fractures are considered to be a multifactorial occurrence, making the study and prioritization of its various factors highly important.

The importance of stroke in the risk of hip fracture started to be raised in 1997, after a study carried out in the Japanese population by Suzuki at al.[1] Subsequent studies[2-5] have reinforced these findings, leading to the consideration of hemiplegic patients as a population at risk, and recommendations for the systematic determination of bone mineral density (BMD) and the use of bisphosphonates during the rehabilitation period[6].

There are various etiopathogenic theories which have tried to explain this outcome, varying from an increase in falls, the consequence of a change in gait[1], to an accelerated reduction in bone mass provoked by immobility[7]. This suggestion has been reinforced by some studies which found significant differences in bone mass between the paretic side and the healthy side, as well as relationships between levels of BMD and residual functional activity[7-9].

Some authors have suggested that the increased risk of fracture is rooted in the vitamin D deficit[10] which patients with hemiplegia usually suffer, a deficit attributable to nutritional deficiencies and low exposure to sun. The impact on bone quality and a greater risk of falls due to muscle weakness could explain the increase in fractures[11].

Genetic alterations have also been blamed, since there may be a greater presence in stroke patients of a polymorphism in the OPG-118c/C gene, which controls the synthesis of osteoprotegerin, although this alteration has only been associated with stroke with hemorrhagic etiology[12].

More recent theories suggest an alteration in bone remodelling, much increased during the first year post-stroke, as the cause of the deterioration in bone quality[13-15].

But it is also possible that those patients who suffer a cerebrovascular accident (CVA) arrive at this outcome with lower levels of BMD and therefore a greater risk of suffering osteoporotic fractures[16].

The explanation of this situation may be found in the relationship, not yet sufficiently clarified, between dyslipemia, arteriosclerosis and osteoporosis, with possible common etiopathogenic mechanisms[17].

The aim of this study was to discover the absolute risk of major osteoporotic and hip fractures using the FRAX® tool in patients with CVA. Our secondary objectives were to try to evaluate the existence of baseline differences in the osteometabolic parameters and BMD between patients with stroke and a control group without cerebrovascular pathology.

Patients and method

A comparative, multicentred, prospective study, was carried out in 50 patients with CVA and 32 controls, due to non-1:1 pairing, with the participation of the rehabilitation services of five Spanish hospitals. The inclusion of patients started in March 2011, ending in June 2013. The study was authorised by the ethics committees for scientific research of the participating hospitals. Due to budget restraints it was not possible to carry out the control group densitometry studies in one centre. All the patients, both in the study group and in the control group, gave their informed consent.

Inclusion and exclusion criteria

a) Group of patients with CVA: the inclusion criteria were:

- Patients referred to the rehabilitation clinic with a diagnosis of CVA of at least 3 months development, whether there was etiology ischemic or hemorrhagic.
- Aged between 60 and 80.

The following were established as exclusion criteria:

- Patients who, prior to the stroke, were bedridden, due to any pathology, for more than 24 weeks.
- Patients who were non-ambulant prior to the stroke.
- Previous CVA with functional impacts.
- Patients diagnosed with secondary osteoporosis due to hiper- or hypoparathyroidism, hipo- or hyperthyroidism, hypogonadism in males, treatment with oral corticoids for more than 3 months, chronic alcoholism with the presence or hepatic alterations.

b) Control group:

This was made up of patients who attended the rehabilitation clinic for any type of pathology but who did not suffer from a vascular disease (CVA, ischemic cardiac pathology, arterial ischemia in the lower limbs).

The selection was made according to a system which paired age and sex.

The other exclusion criteria were the same as with the CVA group: being bedridden, non-ambulant, secondary osteoporosis.

Variables studied in the CVA group

- Age and sex.
- Ischemic or hemorrhagic CVA etiology.
- Ability to ambulate according to the functional ambulation classification of the of the Hospital of Sagunto (FACHS) which stratifies this activity in the following way:

Level 0: Incapable of, or zero, ambulation.

Level 1: Non-functional ambulation.

Level 2: Ambulation only inside buildings and the home.

Level 3: Ambulation in the surroundings of the home with a perimeter of less than 600 metres.

Level 4: Independent ambulation in the community but with abnormal gait (any type of limp).

Level 5: Normal ambulation without lameness or any limitations.

- History of fragility fractures in the 10 years prior to CVA, and location.

- Number of falls in the year before the stroke.
- BMD in the hip.
- T-score: considered to be osteopenia when between -1 and -2.5, and osteoporosis when T< -2.5.
- FRAX® index: there is considered to be a risk of fracture when the percentage values for major osteoporotic fracture is ≥10 and for hip fracture, ≥3.
- Analytical tests:
* Biochemistry: glucose, cholesterol and triglyceride.
* Bone markers: total alkaline phosphatase, 25-hydroxyvitamin D, PTH, calcium, phosphorus and carboxy-terminal telopeptide of collagen I (CTX) in blood.

In the control group the same data were collected, with the exception of those related to the hemiplegia and functional status.

Statistical analysis

An initial statistical analysis was carried out, calculating the frequencies and percentages of the categorical variables. The comparative statistical study was carried out using contingency tables with residual analysis.

For the quantitative variable the mean plus standard deviation were calculated using the t-Student test to perform the comparative analysis. The level of statistical significance was established at $p<0.5$ for all the variables analysed.

Results

A total of 82 patients were studied: 50 patients with CVA and 32 who made up the control group.

With respect to sex, in the CVA group there were 24 men (48%) and 26 women (52%), with no significant difference in that of the control group which was made up of 14 men (43.75%) and 18 women (56.25%).

There were also no significant differences in the average age of the two groups: CVA: 70.32 years (SD±5.8); and control group: 72.44 years (SD±6.6).

Ischemic processes determined the etiology in 39 cases (91%) and cerebral haemorrhage was diagnosed in 4 (9%); no cause was given in 7 patients.

The majority of patients in the study had an ambulant capability of 3 or 4 on the FACHS (CFMHS) scale (Table 1).

The patients with CVA had suffered a greater number of falls in the year before the study; on the other hand the control group had a greater history of fragility fractures (Table 2).

T-score at hip: 66% of stroke patients and 50.15% in the control group had a T-score levels of osteopenia or osteoporosis, with no significant differences between groups (Table 2).

BMD in the hip: The hemiplegic patients had a lower average level of bone mass in the hip than the control group, but the differences were not significant (Table 4).

FRAX® index: In the control group the number of patients with a high risk of suffering a fragility fracture was higher than in the CVA group, although the differences were not statistically significant (Table 2).

Biochemical tests: Levels of cholesterol were higher in the control group, but not glycemia or triglycerides, the differences not being significant in any case (Table 3).

Analytical markers for bone metabolism: Levels of vitamin D: In the CVA group 32 patients (68%) had levels lower than 30 ng/ml, classed as vitamin D insufficiency or deficiency; in the control group 22 patients (71%) were insufficient or deficient in this vitamin. The differences between the groups was not significant.

There were also no significant differences found in the values of calcium, phosphorus and PTH.

The levels of CTX were significantly higher in patients with CVA (Table 4).

Discussion

This study was intended to show the baseline in relation to the risk of osteoporotic fracture of patients who had suffered a recent CVA, on the assumption that most of the findings will be more related to their pathological history and life style, than to the impact which, with the passage of time, a stroke could have on the bone system, with motor repercussions. As might be expected, in the majority of patients the stroke had an ischemic etiology, a rate of 91% being the highest of the rates found in the neurology services[18], although it is possible that the higher mortality of the hemorrhagic stroke results in a greater proportion of ischemic strokes in the rehabilitation services.

To evaluate functional status we used the FACHS (CFMHS)[19], which is a valid scale and widely used in rehabilitation services. We preferred this to other better known scales such as the Barthel Index, because it focuses on the ambulatory capability of the patient, the daily activity most relevant to development of bone health.

In relation to the results obtained with this scale of ambulation, we believe it is important to to highlight the fact that while it may be limited, 62% of stroke patients have autonomous ambulation, a surprising situation in acute phase CVA, although there may be a selection bias due to the difficulties (transport, tests, etc) which those patients with the most sever motor impairments may have.

We have chosen the FRAX® index because, in spite of some of its recognised limitations, it is increasingly being used a tool. A cut off point of 10 was established for major osteoporotic fracture, and 3 for establishment of a high risk of hip fracture, due to these being the minimum cut off values which, when the study started, were recommended and used by other Spanish authors[20,21]. While there is increasing evidence that the FRAX® index underestimates the risk of fractures in the Spanish population, major osteoporotic fractures in particular, although the prediction of hip fracture is more sensitive[22], we should emphasise that this is the index most relevant to our study.

Using these cut off levels, we found that 12% of patients had a high risk of suffering a hip frac-

Table 1. Capacity ambulation following FACHS

	Frequency	Percentage
Level 0: No ambulation	7	15.21%
Level 1: No functional ambulation	3	6.50%
Level 2: Only at home	7	15.21%
Level 3: Independent perimeter less than 600 meters	13	28.26%
Level 4: Separate up to ANOMALOUS	12	26.08%
Level 5: Normal ambulation	4	8.69%
Was not collected	4	8.6%

ture, and 8% of suffering a major osteoporotic fracture in the next 10 years. We found no similar studies in patients with stroke with which we were able to compare our results.

In terms of the values of BMD in the femoral neck, 58% of stroke patients had osteopenia and 8% osteoporosis. A study published by Hye Won[16], carried out in patients with the same characteristics as ours (acute phase CVA), found rates of osteopenia and osteoporosis in the spine of 39% and 43% respectively, although we should remember that, according to studies carried out by Díez Curiel, the reduction of BMD is more common in the spine than in the hip[23].

It may appear surprising that the control group, despite being similar in sex and age to the patients with CVA, have a greater risk of suffering a major osteoporotic or hip fracture, a situation which may be correlated with a greater number of fragility fractures in the 10 years prior to the study. But this finding could make one suspect selection bias and therefore a limitation to our results, which has favoured the inclusion of patients with osteoporosis in the control group. We should not forget the fact that the prevalence of osteoporosis in a general rehabilitation clinic is very high, as Serralta[24] reported, finding this pathology in 53% of his patients.

The relationship between dyslipemia and bone metabolism has been described by various authors, but without conclusive findings[17]. In our study we found no significant differences from the control group in any of the biochemical parameters. In absolute terms, the rates of cholesterol were lowest in the patients with CVA. These results need to be treated with caution since we did not record possible lipid-regulating treatments, which is a limitation of the study, especially given the significant effects the statins appear to have on bone metabolism and in the reduction in risk of fractures[17].

What is notable is the significant number of patients with vitamin D insufficiency or deficiency in both groups, a finding which points once again to prevalence of the deficiency in this hormonal system in Spain, which is found in 30% of the general population, reaching to 87% in institutionalised older people[25,26].

The most significant of the analytical findings is the increase in the marker for bone resorption CTX in the group with stroke. This finding has been reported in other studies which, like ours, have been carried out in acute phase stroke patients[15] an which correlates with a greater loss of bone mass in the hip[13].

For these authors there is a correlation between high levels of CTX and the degree of motor impairment; in this case mechanostasis would be the most influential factor in the increase in bone resorption in these patients. However, bone metabolism is a complex process in which local and endocrine-metabolic factors are involved with a possible final effect on RANK-RANKL-OPG, which would be the final agent of the bone remodelling process[27].

It is possible that, similar to changes in this system which have been described in Paget's disease, prostate cancer or osteoid arthritis, among others[27], some specific changes in these cytosines may be found in patients with CVA.

In conclusion, if we want to reduce the risk of patients with CVA suffering a hip fracture in the years following a stroke, a programme of physical therapy with load and ambulation should be planned to favour mechanostatic factors, without forgetting the need for antiresorptive treatment, at least for patients in whom a risk of fracture is detected.

Conflict of interest: The authors declare that there are no conflicts of interest.

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Table 2. Frequency and percentage of falls during a year, fractures in the previous 10 years, of patients with osteopenia and osteoporosis in the hip (T-score) and patients with high risk of major osteoporotic fracture (MO) and of hip fracture (HF) in both groups studied

		Fallen	Fractures	T-score: -1 a -2.5	T-score: ≥-2.5	FRAX® MO ≥10	FRAX® HF ≥3
CVA	Frequency Percentage	4 8%	3 6%	29 58%	4 8%	4 8%	6 12.5%
Control	Frequency Percentage	0	8 25%	13 34%	5 15%	4 13%	8 25.8%

Table 3. Biochemical determinations. Averages

	CVA	Control	p value
Glycemia (mg/dl)	108.97	99.68	NS
Cholesterol (mg/dl)	144.97	199.48	NS
Triglycerides (mg/dl)	129.7	114.33	NS

Table 4. Bone mineral density (BMD) of the hip bone and biochemical parameters

	CVA mean±SD	Average control±SD	p value
BMD hip (g/cm²)	0.7216±0.185	0.7609±0.16	NS
Calcium (mg/dl)	9.37±0.46	9.42±0.58	NS
Phosphorus (mg/dl)	3.54±0.70	3.37±0.56	NS
Total alkaline phosphatase (UI/l)	125.32±67	111.97±52	NS
Vitamin D (ng/l)	25.31±11	24.69±11	NS
PTH (pg/ml)	48.73±35	59.99±36	NS
CTX (ng/ml)	0.4362±0.27	0.2907±0.11	0.011

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