

Original Article

Effect of alendronate on bone mineral density in spinal cord injury patients: a pilot study

CM Moran de Brito^{*1}, LR Battistella^{1,2,3}, ET Saito¹ and H Sakamoto¹

¹Department of Rehabilitation Medicine of the University of São Paulo Hospital das Clínicas, São Paulo, Brazil;

²University of São Paulo, São Paulo, Brazil; ³International Society of Physical Medicine and Rehabilitation (ISPRM), São Paulo, Brazil

Study design: Prospective, randomised controlled trial.

Objective: To evaluate the effect of alendronate on bone mineral density in chronic spinal cord injury (SCI) patients.

Setting: University-based rehabilitation centre in São Paulo, Brazil.

Methods: A total of 19 chronic SCI patients were evaluated, divided into a control group and an experimental group. Control group patients received 1000 mg of calcium daily, and experimental group patients received 1000 mg of calcium plus 10 mg of alendronate daily. The study duration was 6 months. In all, 12 densitometric parameters were analysed using whole-body dual-energy X-ray absorptiometry at baseline and after 6 months.

Results: The experimental group presented increases in nine densitometric parameters, although statistical significance was attained in only two of those parameters. In the control group, an increase was observed in only one parameter, whereas the remaining 11 presented either no alteration or a decrease.

Conclusion: The use of alendronate had a positive effect on bone mineral density in SCI patients and therefore represents a potential tool for prevention and treatment of osteoporosis in this population.

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Introduction

Osteoporosis is a well-known chronic complication of spinal cord injury (SCI).^{1–12} However, many challenges remain, such as gaining a better understanding of the physiopathology and optimising management. Bone loss mechanisms in SCI are not completely understood.^{1,3,4} In SCI, a significant portion of bone loss occurs during the first 4–6 months after injury (30% within the first 3–4 months) and stabilises between the 12th and 16th months.^{1,2,5,6} Bone loss initially affects the whole body and is later restricted to paralysed areas.^{7–10}

Lack of mechanical stress is certainly involved in, but cannot be held solely responsible for, the intensity of bone loss. Neurovascular changes secondary to modification of the autonomic nervous system, as well as resistance to or decreased levels of insulin-like growth factor 1, have been implicated in this process.¹³ The fact that the bone loss seen in SCI is more intense than that resulting from immobility can be attributed to the

complexity of the mechanisms involved.⁵ It has also been suggested that SCI may cause structural changes in collagen, inducing increased resorption.^{6,13} Immobilisation-related bone loss was first described in 1941 by Albright *et al*¹⁴ as an atrophy of the bone, simulating hyperparathyroidism. As a result of the bone loss, there is decreased bone density and a consequent increase in fracture risk. The incidence of pathologic long-bone fractures in SCI has been reported to be between 1 and 7%.^{15–25} Such fractures typically result from minor traumas occurring during daily activities,¹⁶ stretching exercises,¹⁷ transfers,¹⁸ or the use of functional electrical stimulation (FES).¹⁹ In the majority of cases, the patient has no recollection of the trauma mechanism.²⁰

Regarding prevention and treatment of osteoporosis in SCI patients, no effective management strategy has been established to date. Studies endeavouring to evaluate the role of orthostatism and exercise as a means of treatment and prevention have produced inconclusive results.^{26–37} Most studies using FES have shown little or no change in bone density.^{31,33,34,36}

*Correspondence: CM Moran de Brito, Avenida Angélica, 1968 9º andar, Consolação Cep: 01228-200 São Paulo-SP, Brazil

The results of some studies have suggested local benefits.^{32,35,37}

As far as medical treatment is concerned, the use of bisphosphonates constitutes a safe and effective therapeutic intervention for the treatment of osteoporosis,^{38–40} although there have been very few studies involving SCI patients.^{41–44} The mechanisms of action of bisphosphonates such as alendronate, clodronate, etidronate, pamidronate, risedronate, and tiludronate include reduction of bone resorption through osteoclast inhibition and long-term reduction of the number of osteoclasts. The bisphosphonate etidronate also interferes with bone mineralisation and is therefore used cyclically in order to avoid this undesirable effect.

Pearson *et al*⁴¹ evaluated the effect of cyclic etidronate (2-week regimens of 800 mg a day, with a 13-week interval intervening) for 30 weeks (two cycles) in six SCI patients compared with seven SCI controls and found benefit for those that recovered mobility. Minaire *et al*⁴² studied the effect of dichloromethylene in 21 paraplegic patients and concluded that it can reduce bone loss during the acute phase. Another study included 70 patients with immobilisation-related bone loss and compared different treatments: calcitonin ($n=20$), etidronate ($n=20$), placebo ($n=16$), and clodronate 400 mg/day ($n=7$) or 1600 mg/day ($n=7$).⁴³ The authors found that calcitonin and the 1600 mg/day dose of clodronate appeared to be the most effective for inhibiting bone resorption. Chappard *et al*⁴⁴ studied the effect of 200 and 400 mg/day of tiludronate in 20 paraplegic patients and found that, compared to controls, patients benefited from 400 mg/day of tiludronate.

In their favour, bisphosphonates also act specifically on the bone tissue and have minimal side effects, which can include gastrointestinal disturbances and (quite rarely) hypersensitivity reactions.³⁸

Prevention and treatment of osteoporosis through pharmacological means shows promise. Such treatment should, ideally, be introduced early since orthostatism and exercise alone have not been proven effective. Szollar²¹ suggested that preventive intervention should be initiated approximately 1 year after injury and, should the densitometric evaluation show significant bone loss before that period, treatment should be started even earlier. The author also suggested semestral densitometric evaluation.

Bearing in mind the above findings, together with those of the few studies evaluating the use of bisphosphonates in managing osteoporosis in this group of patients, this study was undertaken with the objective of evaluating the effect of alendronate on bone mineral density (BMD) in chronic SCI patients. The aim was to assess alendronate as a possible therapeutic intervention for minimising the accentuated bone loss that occurs in these patients and the complications arising from the same. It should be emphasised that alendronate has been proven to be safe and effective in the treatment of osteoporosis in both men and women and has been approved by the Food and Drug Administration.³⁸

Methods

Study design and procedure

A controlled randomised clinical study was conducted in order to compare SCI patients treated with alendronate and calcium (experimental group) with SCI patients treated with calcium alone (control group). The patients were recruited from those treated at the Spinal Cord Outpatient Clinic of the Department of Rehabilitation Medicine of the University of São Paulo during the period from May to September of the year 2000.

In order to eliminate any influence of voluntary mobility, the study included only patients with SCI for more than 6 months and presenting class A, B, or C injuries as designated by the American Spinal Injury Association (ASIA) classification system.⁴⁵ Both female and male patients were included, although age cutoffs were imposed (35 for females and 50 for males) in order to avoid the physiological bone loss period. Subjects were excluded if presenting any of the following conditions: active heterotopic ossification; renal, metabolic or liver disease; alcoholism; pregnancy; breast feeding; chronic use of steroids, heparin or anticonvulsants; smoking; or recent radiological exposure. Patients were submitted to initial clinical evaluation (interview and physical examination) and laboratory tests in order to rule out secondary causes of osteoporosis.

Control group patients received 1000 mg of calcium daily, divided in two doses. Patients in the experimental group also received 1000 mg of calcium daily, divided in two doses, plus a daily dose of 10 mg of alendronate. Patients in both groups continued these regimens, without interruption, for 6 months. The patients who received the alendronate were instructed to take it with water on an empty stomach, not to lie down for at least 30 min after having taken the medication and not to take any other medicine, including the calcium, simultaneously. Patients were submitted to densitometric evaluation at the study onset and again at the study end point (after 6 months). In addition, all patients were examined, on a monthly basis, throughout the study period. Whole-body bone density was measured through dual-energy X-ray absorptiometry (DEXA) using a Lunar Model DPX (Lunar Corp., Madison, WI, USA). The Ethics Committee of the University of São Paulo Hospital das Clínicas approved the experimental protocol, and all participating patients gave written informed consent.

Measurements and analysis of data

Bone loss was assessed through evaluation of the following three bone density parameters: BMD (expressed as g/cm²); *T* index (variation in relation to young adults; expressed as mean and standard deviation, SD); *Z* index (variation in relation to individuals in the same age bracket; expressed as mean and SD). In addition to whole body measurements, upper-extremity (UE), lower-extremity (LE), and trunk measurements were also taken.

Subsequent to the initial measurements, the means were compared using Student's *t*-test with the purpose of assuring that both groups of patients would be comparable in terms of the features of interest to the researcher and determining whether the randomisation had been successful. Variations between initial and final bone density measurements were then calculated, as was the mean of the difference in variation of all bone density parameters. The means of variation of both groups were compared using Student's *t*-test (null hypothesis: the means of variation of both groups would be equal). The level of statistical significance adopted was $P < 0.05$. The statistical analysis was carried out using the statistical data analysis software program STATA, version 7.0 (Stata Corp., College Station, TX, USA).⁴⁶

Results

A total of 19 patients were included in the study. In all, 10 patients were randomised to receive alendronate, and nine were randomised to the control group. Each group included two women, corresponding to 22.2% of the control group and 20% of the experimental group ($P = 0.91$). The two groups were also similar in age, weight, and time since injury (Table 1).

Regarding the degree and nature of the injury, the control group consisted of four paraplegics and five quadriplegics, among whom there were four victims of automobile accidents, three gunshot victims, and two victims of falls. The treatment group consisted of eight paraplegics and two quadriplegics, among whom there were five victims of gunshots, two victims of automobile accidents, three victims of falls, and one victim of an infectious disease. All patients tolerated 10 mg of alendronate without any reported adverse effects. One

patient in the control group presented constipation that was promptly managed with conservative treatment.

Two patients (one in each group) interrupted their participation in the study and were not submitted to the final densitometric evaluation and were thus excluded from the final data analysis. One of those two patients moved to another city during the treatment period, and the other failed to report for the monthly appointments from the 3rd month onwards because of a job change.

Mean initial BMD measurements were similar for all body segments in both groups. Mean *T* and *Z* indexes obtained in the original evaluation were also comparable. In both groups, initial LE indexes were the lowest and were lower in the experimental group patients than in the controls. In contrast, initial UE indexes were the highest in both groups.

After 6 months of treatment, patients in the experimental group presented increased bone density in nine of the 12 parameters analysed. In the three remaining parameters (LE BMD, total BMD, and LE *T* index), there was practically no variation. In the control group patients, only the LE *Z* index showed a positive variation, whereas there was either no change or a loss of bone density in the remaining parameters. The greatest difference in variation between the two groups was found in the UE *T* index, in which control group patients presented a mean loss of 0.63 and experimental group patients presented a mean gain of 0.29 (Table 2). The least difference in variation was found in the LE index.

Comparison of variations in mean UE BMD showed that there was a consistent increase in bone density in patients treated with alendronate plus calcium (0.03), whereas control group patients presented greater variability in UE BMD values, which were higher in some and lower in others (mean, -0.03). Mean increase in UE BMD in the experimental group was greater than in the control group in a marginally significant manner ($P = 0.14$; Table 2). No significant difference between the two groups was found in the BMD variation at the trunk ($P = 0.54$). In both groups, there was wide variability, although patients in the experimental group presented an overall gain in bone density. Comparison of variations in LE BMD showed very similar values in both groups ($P = 0.73$), practically unaltered after 6 months. In experimental group patients, there was a small increase in mean total BMD (0.01) that was slightly higher than that seen in control group patients ($P = 0.04$; Table 2). Variations in the *T* index were quite similar to those found in the BMD analysis. In the experimental group, there was a greater increase in the mean UE *T* index (0.29) than in the control group ($P = 0.10$). There was a tendency towards increased trunk *T* indices in experimental group patients (mean, 0.14), whereas trunk *T* indices presented a downward trend in control group patients (mean, -0.16), although the difference was not statistically significant ($P = 0.18$; Figure 1). Comparison of variations in LE *T* indices revealed little change in either group ($P = 0.28$). In the comparison of variations in total *T* indices, we observed

Table 1 Age, weight and time since spinal cord injury in patients included in the study ($n = 19$)

	Control group ($n = 9$)	Experimental group ($n = 10$)	P-value
Age (years)			0.98
Mean	30.8	30.9	
SD	9.9	9.5	
Minimum– maximum	17–47	18–46	
Weight (kg)			0.62
Mean	75.2	72.7	
SD	12.6	9.2	
Minimum– maximum	56–100	57–73	
Time since injury (months)			0.39
Mean	38.7	61.0	
SD	17.1	77.3	
Minimum– maximum	22.8–77.5	13.1–255.7	

Table 2 Results of initial and final bone density measurements of control and experimental groups

	Control group (CG) (n=8)			Experimental group (EG) (n=9)			Mean variation between groups CG-EG	P-value
	Initial measures mean (SD)	Final measures mean (SD)	Variation mean (SD)	Initial measures mean (SD)	Final measures mean (SD)	Variation mean (SD)		
BMD-UE (g/cm ²)	0.97 (0.14)	0.94 (0.09)	-0.03 (0.09)	0.96 (0.07)	0.99 (0.08)	0.03 (0.08)	-0.06	0.14
BMD-trunk (g/cm ²)	0.94 (0.09)	0.93 (0.07)	-0.01 (0.13)	0.94 (0.11)	0.96 (0.11)	0.02 (0.14)	0.03	0.54
BMD-LE (g/cm ²)	1.07 (0.20)	1.06 (0.18)	-0.01 (0.05)	1.02 (0.17)	1.01 (0.15)	0.01 (0.02)	0	0.73
BMD-total (g/cm ²)	1.12 (0.11)	1.11 (0.10)	-0.01 (0.02)	1.10 (0.09)	1.11 (0.08)	0.01 (0.02)	-0.02	0.04
T index-UE	0.31 (1.67)	-0.32 (0.84)	-0.63 (1.25)	0.16 (0.49)	0.45 (0.72)	0.29 (0.63)	-0.92	0.10
T index-trunk	0.74 (1.54)	-0.90 (1.30)	-0.16 (0.38)	-0.59 (1.51)	0.45 (1.57)	0.14 (0.41)	-0.31	0.18
T index-LE	3.10 (2.36)	-3.20 (2.32)	-0.10 (0.60)	-3.71 (1.63)	3.73 (1.28)	0.02 (0.48)	0.08	0.28
T index-total	0.94 (1.62)	-1.10 (1.58)	-0.16 (0.31)	-1.40 (0.92)	1.27 (0.84)	0.14 (0.23)	-0.30	0.04
Z index-UE	0.29 (1.52)	-0.15 (0.85)	-0.44 (0.92)	0.13 (0.30)	0.46 (0.54)	0.33 (0.65)	-0.77	0.09
Z index-trunk	0.78 (1.46)	-0.78 (1.28)	0 (0.35)	-0.48 (1.08)	0.09 (1.16)	0.38 (0.73)	-0.38	0.26
Z index-LE	3.01 (2.44)	-2.96 (2.33)	0.05 (0.90)	-3.62 (1.74)	3.55 (1.42)	0.07 (0.51)	-0.02	0.97
Z index-total	0.87 (1.58)	-1.01 (1.45)	-0.13 (0.51)	-1.39 (0.84)	1.18 (0.75)	0.21 (0.29)	-0.34	0.11

BMD: bone mineral density; LE: lower extremities; SD: standard deviation; UE: upper extremities

an increase in the experimental group (mean, 0.14) and an overall decrease in the control group (mean, -0.16; $P = 0.04$; Figure 2; Table 2). In addition, the comparison of variations in the UE Z index showed a marginally significant difference between the two groups, increased in the experimental group (mean, 0.33) and decreased in the control group (mean, -0.44; $P = 0.09$; Table 2). No statistically significant difference was found between the groups in trunk Z index variation, although patients in the experimental group also presented a mean increase in this index. Comparison of variations in the LE Z index revealed no significant differences between the groups ($P = 0.97$). Patients treated with calcium plus alendronate presented greater increases in this index and less intragroup variability when compared to those treated with calcium alone. Finally, there was a marginally

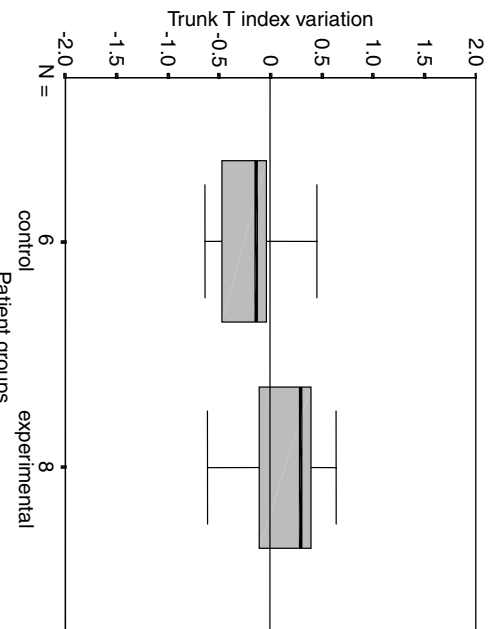


Figure 1 Comparison of variation of the T index of the trunk between the experimental and the control group ($P = 0.18$)

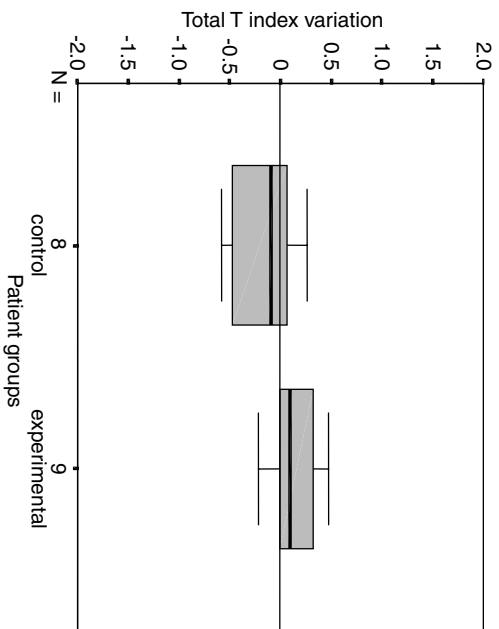


Figure 2 Comparison of variation of the total T index between the experimental and the control group ($P = 0.04$)

significant difference between the two groups in terms of total Z index variation, in which the experimental group presented an increase (mean, 0.21), whereas the control group presented a decrease (mean, -0.13; $P=0.11$; Table 2).

Discussion

Ideally, a study of bone metabolism should include measurement of biochemical reabsorption and determination of bone formation marker levels,^{47–58} which are more sensitive than bone densitometry, as has been shown by Machado *et al*.⁵⁹ The authors compared the sensitivity of biochemical markers with that of bone densitometry in the evaluation of alendronate treatment in 26 postmenopausal women. They determined that the benefit for patients in the treated group, in comparison to controls, was statistically significant ($P<0.01$) in five of the six biochemical markers evaluated but in only two of the six regions evaluated by the densitometry. The authors also suggested that densitometric measurements should be taken 1 week before and after treatment in order to reduce short-term variability. However, these results corroborate the consensus in the literature that DEXA is a highly precise and reproducible method.^{60–64} In contrast, Liu *et al*,⁶⁵ in a study of 64 chronic SCI patients, postulated that quantitative computed tomography is more sensitive than DEXA in evaluating spinal osteoporosis following SCI.

One of the main methodological limitations of the present study is the small number of subjects studied. Although patients in the experimental group performed better in the majority of bone density parameters, a satisfactory level of statistical significance was achieved in only two of those parameters. However, our findings suggest that treatment with alendronate can improve densitometric measurements. Another limitation is the fact that only initial and final bone density measurements were obtained. Therefore, we can only estimate the pattern of the effect of alendronate on bone mass. For example, the alterations in bone mass may occur in a constant form over time or may only begin some months after the initiation of treatment.

Ideally, the duration of treatment time should be longer, which would allow a more accurate evaluation. However, in the Fosamax International Trial,⁵⁴ carried out in 153 centres in 34 countries and involving a total of 1908 patients with postmenopausal osteoporosis, sodium alendronate was compared to a placebo through analysis of biochemical markers and densitometric parameters. The authors found a considerable statistically significant difference between the two groups after 3 months of treatment, both in relation to biochemical markers and densitometric indices (lumbar spine and femur), and a progressive difference throughout the first year. Rossini *et al*⁶⁶ obtained similar results when evaluating daily administration of 20 mg of alendronate for 6 months to 15 patients with postmenopausal osteoporosis, showing a 4.6% gain in bone mass at the lumbar spine level after 1 year. In addition, Adami *et al*⁶⁷

compared daily administration of 10 mg (68 patients) and 20 mg (72 patients) of alendronate for 1 year and showed 4.4 and 5.8% gains in bone mass, respectively, at the lumbar spine level. In the present study, the best response to alendronate was achieved at the UE level, suggesting that treatment response is variable, and areas with functional mobility might present a greater response. Supplementary vitamin D, together with calcium, is indicated by some authors, but it is only advisable in elderly patients or patients with vitamin D deficiency.

Bearing in mind the evolution and particularities of the osteoporosis occurring in SCI patients, one should pay special attention to the time of injury when evaluating patients presenting similar rates of bone loss and comparing different therapeutic interventions. Intervention must, ideally, be introduced early, as a large portion of bone loss occurs within the first 16 months. During the first year, bone loss in paralysed areas is approximately 4% per month in areas rich in trabecular bone and 2% per month in those rich in cortical bone. In the upper portion of the tibia, an area particularly rich in trabecular bone, bone loss reaches 50% after 18 months, compared with 20% in the area close to the femur during the same period.⁹

Fracture incidence is considerable in SCI patients and may lead to autonomic dysreflexia, deformity promoting pressure ulcers, and additional loss of function. In such patients, fracture diagnosis is more challenging due to the sensory and functional deficits already present.¹⁶ Minor symptoms such as local sweating, oedema, and increased spasticity might be the only indications of fracture.¹⁸

Lazo *et al*¹⁵ found that risk of fracture is at least doubled for each unit decrease in T index BMD SD at the femoral neck, and concluded that measurement of BMD at this site can be used to quantify fracture risk in SCI patients. Szollar *et al*²² compared BMD measurements of 176 SCI patients with those of 60 patients with no injury. The authors studied the lumbar spine and femoral areas and found a significant decrease in bone density, reaching fracture thresholds after 1–5 years. However, in the lumbar spine, there was no significant decrease, either in quadriplegic or paraplegic patients. Dissociation of demineralization between the spine and pelvis is considered a typical finding in SCI patients,^{3,4,8} in contrast with endocrinopathies, which lead to greater bone loss at the spine. It has been suggested that relative preservation of bone density at the spine is due to the load provided by the sitting position.⁸

Regarding treatment, there have been few studies to date evaluating the use of kinesiotherapy. The few studies available typically involved small patient samples and short follow-up periods, which makes it difficult to evaluate possible benefits. Kunkel *et al*,²⁶ in a study involving a group of SCI patients, found no benefit from 90 min per day of orthostatism with the use of an orthostatic board. Saltzstein *et al*²⁸ evaluated subjects with complete and incomplete SCI in order to determine whether there was a correlation between mobility and

bone density and stated that SCI individuals benefit from making efforts to stand with some regularity. Goemaere *et al*²⁹ reported that subjects standing regularly, starting 1 year after SCI, had more well-preserved BMD than did age- and sex-matched controls. In addition, de Bruin *et al*³⁰ suggested that an early exercise programme in which standing exercises are combined with walking seems to reduce the expected rate of bone loss in SCI patients, although the authors found no difference between combined early standing and walking and early standing only.

Studies involving FES have also yielded inconclusive results and very few have used acceptable methodology.^{31–37} Sipski *et al*³² evaluated the use of FES of the lower extremity muscles for 1 h five times a week plus half an hour three times a week on a REGYS[®] bicycle ergometer in two patients and observed some relative reduction of bone loss at the femur. Mysiw *et al*³³ evaluated the use of 12 weeks of FES-induced bicycle ergometry in five patients and observed a reduction in hypercalciuria but not in bone loss intensity. Leeds *et al*³⁴ evaluated the use of FES-induced bicycle ergometry for 6 months and found no significant benefit in terms of reduced bone loss. In contrast, Needham-Shropshire *et al*³¹ evaluated the effect of the use of the PARASTEP[®] system (an orthosis with FES) in paraplegic patients and observed no reduction in the intensity of bone loss. In addition, Mohr *et al*³⁵ observed increased BMD in the proximal tibia but not in the femoral neck or lumbar spine, suggesting site-specific changes. Furthermore, BeDell *et al*³⁶ studied the effects of FES-induced lower extremity cycling on the bone density of 12 chronic SCI patients and found no significant increase in bone density at the hip and some relative increase at the lumbar spine. Moreover, Bélanger *et al*,³⁷ after studying 14 SCI subjects for 24 weeks, concluded that osteopenia of the distal femur and proximal tibia could be partly reversed through the use of FES.

There have also been very few studies involving pharmacotherapy.^{41–44,68–70} However, pharmacological intervention, particularly with bisphosphonates, appears to be a promising strategy. In a recent published study, the effects of long-term treatment with alendronate in a group of paraplegic men were evaluated in a prospective randomised controlled study.⁶⁸ Bone loss was stopped at all cortical and trabecular intralesional sites over 24 months with alendronate 10 mg daily. Sniger and Garshick,⁶⁹ also reported good results with the use of alendronate during 2 years in one patient with incomplete ASIA class D SCI. Calcitonin also represents an alternative, but further studies are needed in order to evaluate its role and benefits.⁷⁰

Conclusions

Our results support the contention that bone loss can be safely attenuated in SCI patients through the use of antiresorptive therapy in the form of oral alendronate. Alendronate administration had a positive effect on

BMD and therefore represents a potential tool for prevention and treatment of osteoporosis in this population. Prevention and treatment of reduced bone density is an important goal and is likely to prevent additional functional impairment and morbidity that might result in fracture. In order to justify the use of alendronate in SCI patients and analyse the cost-benefit relationship, further studies, including larger samples and longer follow-up periods, are warranted.

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