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Osteoporosis in spinal cord injury: rehabilitation

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DESCRIPTION OF THE EVIDENCE COLLECTION METHODOLOGY:

Articles in the MedLine (PubMed) database and other research sources were reviewed, with no age limit. The search strategy used was based on structured questions in the PICO format (from the initials: Patient, Intervention, Control and Outcome).

The descriptors used were:

QUESTION 1: (spinal cord injury OR spinal cord injuries OR spinal cord trauma OR paraplegia OR tetraplegia OR paraparesis OR tetraparesis) AND (osteoporosis OR bone density OR bone loss OR rarefaction) AND (risk factors OR prevention)

QUESTION 2: (spinal cord injury OR spinal cord injuries OR spinal cord trauma OR quadriplegia OR tetraplegia OR paraplegia) AND (Osteoporosis OR bone density OR bone loss OR rarefaction) AND (calcium consumption OR calcium recommendation OR calcium intake OR dietary calcium)

QUESTION 3: (spinal cord injury OR spinal cord injuries OR spinal cord trauma OR quadriplegia OR tetraplegia OR paraplegia) AND (Osteoporosis OR bone density OR bone loss OR rarefaction) AND (vitamin D OR ergocalciferol OR cholecalciferol)

QUESTION 4: (spinal cord injury OR spinal cord injuries OR spinal cord trauma OR paraplegia OR tetraplegia OR paraparesis OR tetraparesis) AND (osteoporosis OR bone loss OR bone demineralization OR bone density OR rarefaction) AND (physical therapy modalities OR recreation therapy OR exercise OR physical exercise OR physical activity OR physical activities OR movement OR exercise training OR aerobic exercise OR resistance exercise OR exercise therapy OR endurance exercise OR muscle exercise)

QUESTION 5: (spinal cord injury OR spinal cord injuries OR spinal cord trauma OR paraplegia OR tetraplegia OR paraparesis OR tetraparesis) AND (osteoporosis OR bone density OR bone loss OR rarefaction) AND (vibration OR vibration therapy)

QUESTION 6: ("Spinal Cord Injuries" OR "Paraplegia" OR "Quadriplegia" OR "Paraparesis") AND ("Osteoporosis" OR "Bone Diseases" OR "Fractures Bone" OR "Bone Density" OR "Fractures Spontaneous") AND ("Densitometry" OR "Absorptiometry, Photon" OR "Radiography") AND ("Distal Femur")

QUESTION 7: ("Spinal Cord Injuries" OR "Paraplegia" OR "Quadriplegia" OR "Paraparesis") AND ("Osteoporosis" OR "Bone Diseases" OR "Fractures Bone" OR "Bone Density" OR "Fractures Spontaneous") AND ("Densitometry" OR "Absorptiometry, Photon" OR "Radiography")

QUESTION 8: (spinal cord injury OR spinal cord injuries OR spinal Cord trauma OR paraplegia OR tetraplegia OR paraparesis OR tetraparesias) AND (osteoporosis OR bone OR bone mineral OR bone loss OR rarefaction) AND (alendronate)

QUESTION 9: (spinal cord injury OR spinal cord injuries OR spinal Cord trauma OR paraplegia OR tetraplegia OR paraparesis OR tetraparesias) AND (osteoporosis OR bone OR bone mineral OR bone loss OR rarefaction) AND (biphosphonate OR diphosphonates OR prevention OR treatment OR therapeutics OR therapy OR premenopausal OR zoledronic acid)

QUESTION 10: (spinal cord injury or spinal cord injuries or spinal cord trauma or paraplegia or tetraplegia or paraparesis or tetraparesis) AND (osteoporosis OR bone OR bone mineral OR bone loss OR rarefaction) AND (teriparatide)

QUESTION 11: (spinal cord injury or spinal cord injuries or spinal cord trauma or paraplegia or tetraplegia or paraparesis or tetraparesis) AND (osteoporosis OR bone loss OR rarefaction) AND (utilization or prevention or treatment or therapy or therapeutic or eletric stimulation or ultrasound)

These descriptors were used for cross-correlating in accordance with the theme proposed in each topic of the PICO questions. After analysis of this material, articles relative to the questions were selected that originated evidence on which to base the present guideline.

QUALITY OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS:

A: Experimental or observational studies of highest quality.

B: Experimental or observational studies of lower quality.

C: Case studies (uncontrolled studies).

D: Opinion with no critical evaluation, based on consensus; physiological studies, or animal models.

OBJECTIVE:

To provide information on rehabilitation in spinal cord injury patients with osteoporosis

PROCEDURES:

Therapy for spinal cord injury patients with osteoporosis

CONFLICT OF INTEREST:

No conflict of interest declared.

INTRODUCTION

Osteoporosis is defined as a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to bone fragility and increased risk of fractures. Osteoporosis develops as a result of a disorder of the bone remodeling process.

Risk factors for osteoporosis in the general population include non-modifiable components such as age, female gender, race/ethnicity, and genetic factors. Spinal cord injury (SCI) is considered a modifiable element, in which the age at injury, time since injury, extent of neurological injury (complete *vs.* incomplete) and level of injury should be taken into consideration.

Early assessment and ongoing monitoring of bone health are essential elements of care for the SCI patient.

The pathophysiology of bone remodeling in spinal cord injury in both the acute and chronic phases is not well established, despite the problem being recognized for the past 50 years. The lack of use of the limbs seems to be an important factor, but many specialists believe that the immobilization of these patients is a minor factor in the etiology of bone loss in SCI patients. In these subjects, the process of bone loss occurs immediately after the injury, occurring mainly below the level of injury.

1. What are the risk factors that prevention and treatment of osteoporosis are indicated in SCI patients?

The predictor variables for osteoporosis in spinal cord injury are: how incomplete the injury is ($p < 0.0001$), body mass index ($p = 0.0035$), and age ($p = 0.0394$). It is known that in patients with complete SCI the probability is 6.17 times greater of having bone density low enough in the knees to be categorized into the osteoporosic group[1] **(A)**.

Among the risk factors are excessive consumption of alcohol ($p = 0.0518$), and smoking.[1,2] Concern about relative hypogonadism and/or decreased growth hormone and/or growth factors similar to insulin in recent spinal cord injury continues to grow[2] **(D)**.

Recommendation

The following are factors considered predictors and risk factors for osteoporosis in spinal cord injury: the degree of completeness of the injury, body mass index, age, smoking, and consumption of alcohol[1] **(A)**.

2. Should calcium be used in the prevention and treatment of osteoporosis in spinal cord injury patients?

Immobilization after spinal cord injury causes an increase in bone resorption, hypercalciuria, and suppression in parathyroid hormone, increasing the prevalence of osteoporosis in patients with spinal cord injury.

The use of calcium exclusively, either as supplementation or dietetically, does not prevent the reduction of bone mineral density in hip, spine, and distal tibial epiphysis. However, the combination of alendronate and calcium prevents bone loss of > 10% in the tibial trabecular in a 24-month period, with the average consumption reported being 1263 mg +/- 97.3 mg/day. To obtain these results, existing vitamin D deficiency (< 6 ng/ml) was treated. Both in the control and the treatment group adverse events such as diarrhea, constipation, and heartburn were reported. In the calcium group, there was also a report of one case of spontaneous fracture in the foot. Patients treated with alendronate showed total bone mineral density 5.3% higher than the control group and 17.6% higher in the hip[3] **(B)**.

Consumption of calcium can be accomplished by supplementation with calcium carbonate and through dietary calcium. To achieve the recommended calcium through diet, patients should consume 2-3 servings of milk and dairy products (250 ml skimmed milk, or 1 cup of yogurt, or 1 35-gram slice of cheese)[4] **(B)**.

Recommendation

Calcium intake alone does not prevent bone loss in patients with spinal cord injury, even with consumption of the daily recommendation[3] **(B)**.

3. What is the role of vitamin D in the prevention and treatment of osteoporosis in spinal cord injury?

Synthetic analogue of vitamin D (1α D2) at a dosage of 4 µg daily for 24 months, combined with calcium supplementation, 500 mg/day, reduces the loss in bone mineral density measured by dual energy X-ray absorptiometry (DEXA) in the leg. The peak action of this substance occurs six months after the beginning of treatment.[5]

The supplementation of 4 µg/day of the vitamin D analogue (1α D2) showed improvement in bone mineral density of SCI patients, but this should not be the only factor to be considered in these patients[5] **(B)**.

Adequate intake of calcium and vitamin D should be encouraged, as well as considering physical interventions to stimulate bone formation and thus reducing losses.

Recommendation

The use of substances analog to vitamin D, combined with the adequate intake of calcium and vitamin D promotes an increase in bone mass. The results are observed six months after initiation of consumption, extending up to 24 months of supplementation[5] **(B)**.

4. What is the role of exercise in the prevention and treatment of osteoporosis in SCI patients?

Physical activity for more than 60 minutes per week, with similar frequency and duration for activities with upper limb loading, does not result in a difference in bone mineral density (1.05 ± 0.10 *vs.* 1.04 ± 0.08 g/cm^2, $p = 0.7$), nor in bone mineral content (503 ± 79 *vs.* 509 ± 61 g, $p = 0.8$) of the upper limbs of SCI patients and healthy

volunteers respectively. The bone mineral content of the lower limbs of the SCI patients is lower than in healthy subjects (867 ± 252 *vs*. 1328 ± 140 g, $p = 0.0001$), and the average T-score of SCI patients shows that the lower limb and the trochanter present bone mineral density characterized as osteoporotic, and the bone mineral density of the femoral neck and Ward's triangle are at the limits of osteopenia[6] **(B)**.

Recommendation

There is insufficient evidence to prove the benefit of exercise in the prevention and treatment of osteoporosis in spinal cord injury patients[6] **(B)**.

5. When is vibration therapy indicated for prevention and treatment of osteoporosis in spinal cord injury?

The support of the lower limbs on a platform vibrating at a frequency of 35-40 Hz, (with hips elevated in the wheelchair in order to increase weight-bearing on the lower limbs), for 20 minutes 3 times a week for 10 weeks reduces the loss of bone mineral density, compared to orthostasis without vibration, performed for 40 minutes 3 times per week, also for 10 weeks. The loss of bone mineral density with the lower limbs supported on a vibrating platform was -5.84%; while orthostatic, without vibration -8.36%; whereas when orthostatic on a vibrating platform for 7 minutes, 3 times per week for 10 weeks, there was improvement in bone mineral density of 5.46%[7] **(C)**.

Exercises using segmental vibration with a frequency of 30Hz in the upper limbs for 5 minutes, 5 times a week for 12 weeks improves the strength and speed of movement in the dominant limb in a test performed with loads of 5%, 8% and 10% of body weight ($p < 0.05$)[8] (**B**). However, there is no statistically significant difference in bone mineral content in the right and left upper limbs during this intervention (right side: before, 250 ± 30; after, 271 ± 55; left side: before, 240 ± 29; after, 249 ± 47)[8] **(B)**.

Recommendation

There is limited evidence to indicate the efficacy of vibration therapy in the prevention and treatment of osteoporosis in SCI patients, due to the lack of high-quality studies that support such a recommendation.

6. Bone densitometry: when should it be requested for osteoporosis in spinal cord injury patients?

There is as yet no fully defined response regarding how and when to perform bone densitometry in SCI patients. Based on the extant literature it was found that bone loss occurs in the acute phase.

The bone mineral density (BMD) test should be performed whenever possible, starting at the acute phase, to obtain a monitoring parameter that enables observation of possible losses over time. A review conducted in 2010 by Charmetant et al.[9] showed divergent findings. Szollar et al.[10] reported that the procedure should be done 12 months after spinal cord injury, but as the peak of resorption occurs between 3-6 weeks, Charmetant et al.[9] suggest that it be performed as early as possible with respect to this period.

The spine and femur (neck and total hip) are the sites most utilized.[11] The BMD test appears not to be sensitive to the detection of bone loss in the spine. Baumann et al.[12] found bone loss in the spine of SCI patients when performing quantitative CT. Other studies also show that the technique can influence the results, and that acquisition at the posteroanterior position may overestimate bone mass as it captures substantial cortical bone and possible osteo-degenerative alterations and even calcification in the aorta. The lateral position would be more suitable, but presents technical limitations.[13] It is important to note that even with bone loss, this is not a site of fractures in this population.[13-15]

Recommendation

Despite the need for further studies, whenever possible, BMD tests are recommended, beginning at 3-6 weeks post-injury. The tests may be repeated every year to evaluate the effectiveness of ongoing treatment, and in all cases where the patient has already presented with fracture.

The test sites should include the femur (neck, proximal and distal femur) and the tibia. The presence of heterotopic ossification should be observed and such sites should be excluded from scanning (for example, if there is HO in the right femur, electing the left femur for analysis is recommended).

7. At what value of T score is prevention and treatment of osteoporosis indicated in SCI patients?

The World Health Organization defines osteoporosis as a T-score less than -2.5 and osteopenia as a T-score between -1.0 and -2.5 in the spine, hip and forearm.[16] This same definition has been used to identify osteoporosis in spinal cord injury[16] **(D)**.

Recommendation

There are no established T-score values for SCI patients that indicate prevention or treatment of osteoporosis in this population. Therefore, it is suggested that the T-score parameters predefined for osteoporosis by the World Health Organization be used.[16]

8. What is the role of alendronate/risedronate for osteoporosis in spinal cord injury?

The combination of daily doses of alendronate, 10 mg orally, and 500 mg of calcium for twelve months **(B)** and 24 months,[3,17] **(B)** prevents the loss of bone mineral density in the distal epiphysis of the tibia during the treatment period ($p = 0.017$). In contrast, the exclusive use of calcium 500 mg daily for the same period does not prevent an equivalent loss, with -10.8 ± 2.7% after 24 months compared to the start of treatment ($p > 0.001$)[18] **(B)**.

Constipation, diarrhea, heartburn, transient retrosternal pain, dizziness, and chronic headache occurred in patients using alendronate and calcium.[18] In patients taking calcium only, diarrhea, constipation, and heartburn were observed.[18]

Recommendation

Daily use of combined alendronate 10 mg and calcium 500 mg is recommended. The dosage can also be taken as 70 mg once per week[17,18] **(B)**.

9. Is there benefit with the use of zoledronic acid and other bisphosphonates for the prevention and treatment of osteoporosis in spinal cord injury?

The use of zoledronic acid, 4 mg administered intravenously once per year, showed a significant difference in the reduction of bone mineral density in the lumbar spine ($p = 0.033$), hip ($p = 0.028$) and trochanter ($p = 0.005$).[19] Myalgia, fever, and nasal congestion were observed[19] **(B)**.

The early use of clodronate, taken orally at a dosage of 400 mg/day or 1600 mg/day for 100 days, beginning 5 to 29 days after spinal cord injury, prevents the bone loss associated with acute immobility[20] **(B)**. Similarly, the early use of two cycles of etidronate in a dosage of 800 mg/day orally for two weeks of 15 weeks, six weeks after spinal cord injury, prevents osteoporosis in patients who acquire ambulatory status[21] **(B)**. Similarly, pamidronate via intravenous infusion at a dosage of 30 mg once per month for six months, administered in patients within the first six months after spinal cord injury, reduces to a significant degree the loss in bone mineral density ($p < 0.02$)[22] **(B)**. The improvement is significantly higher in patients with ambulatory ability ($p < 0.05$)[22] **(B)**. Thus, the use of pamidronate in SCI patients capable of walking prevents the loss of bone mineral density[22] **(B)**. Yet the use of pamidronate, 60 mg intravenous, combined with dietary calcium (700 mg/day) and vitamin D does not prevent bone loss in long-term SCI patients with complete motor injury of less than 2.5 months, despite reducing the loss of bone mass[23] **(B)**.

The use of tiludronate at a dosage of 400 mg/day for three months is better than a dosage of 200 mg/day or placebo for reducing the decrease in bone mineral density of the hip and knee, without adverse effects on bone mineralization in paraplegic men[24] **(B)**.

Recommendation

The use of 4 mg of zoledronic acid administered intravenously once a year is recommended[19] **(B)**. Other bisphosphonates such as clodronate, taken orally at a dosage of 400 mg/day or 1600 mg/day; two cycles of etidronate at a dosage of 800 mg/day orally for two weeks of 15 weeks; pamidronate via intravenous infusion, at a dose of 30 mg once per month for six months, administered in patients within the first six months after spinal cord injury, particularly patients with ambulatory capacity, reduces to a significant degree the loss in bone mineral density. Tiludronate at a dosage of 400 mg/day for three months also reduces the decrease in bone mineral density of the hip and knee, without adverse effects on bone mineralization[20-24] **(B)**.

10. What is the role of teriparatide in the prevention and treatment of osteoporosis in SCI patients?

Teriparatide, a form of parathyroid hormone produced by recombinant DNA techniques (PTH 1-34), is an anabolic agent that enhances function of osteoblasts and osteocytes, while also increasing the differentiation of the pre-osteoblasts into osteoblasts. Teriparatide at a dosage of 20 µg per day, subcutaneously, combined with robot-assisted exercise 3 times a week for 6 weeks, followed by 6 months of treatment with teriparatide only, did not improve BMD in the spine or the hip[25] **(C)**.

Recommendation

The combination of treatment with teriparatide with robot-assisted exercise does not improve bone mineral density in the spine or hip in SCI patients[25] **(C)**.

11. Does use of mechanical techniques prevent bone loss in patients with spinal cord injury?

The use of functional electrical stimulation (FES) cycle ergometer in acute SCI (average of 4.5 weeks post-injury), with progressive training for 30 minutes, 3 times per week, for 6 months did not prevent the reduction of bone loss in the tibia[26] (**B**). The loss of bone mineral density in the distal femur can be attenuated in the acute phase with FES-cycle training, however these benefits are not maintained after three months[27] **(B)**. Similarly, FES applied to the lower limb muscles for 15 minutes in each limb twice daily, 5 times a week for 5 months improves the overall DEXA measurements during the three months of treatment ($p < 0.01$), but not after this period[27] (**B**). There was no effect on the hip or spine[28] **(B)**.

The results of the use of FES-cycle ergometer for SCI are already controversial. Three studies found an increase in BMD at the proximal tibia and distal femur,[29-31] **(B)** however without significant differences in BMD in the hip[32-34] **(B)**. The studies with FES-cycle training (performed for at least 3 to 5 weekly sessions of 30 minutes duration for a 6 month period) increase bone parameters in areas directly related to the stimulated muscles (quadriceps muscles of the thigh, distal femur and proximal tibia). However, there is still controversy about the persistence of benefits after discontinuation of treatment[29,31] **(B)**.

Electrical stimulation

There is greater significant reduction in bone mineral loss in the tibia of the limb treated with electrical stimulation (25%), compared with the non-treated control (10%), in patients with complete spinal cord injury in the acute phase, 4.5 months after injury ($p < 0.05$). Electrical stimulation is performed to promote plantar flexion for 35 minutes with 10-pulse trains, 15 Hz, 667 milliseconds, capable of generating about 60% of maximum torque. The stimuli are provided in a home program, 4 sets daily, with 5 minutes of rest between sets, 5 times a week for 3 years[35] **(B)**. In the treated limb, the decline in BMD remains stable during 1.5 years of treatment[35] **(B)**. There is no significant difference in the values of the middle section of the diaphysis of the tibia, however an increase of 31% in BMD was noted in the distal tibia trabecular in limbs trained for two to three years.[36] **(B)**.

Similarly, there is a case report of complete T4 paraplegia (after injury from a firearm projectile) with a significant reduction of BMD loss in the tibia of the limb treated with vigorous isometric contraction of the soleus muscle, induced by electrical stimulation of 3 pulses of 10 stimuli, 15 Hz, in 4 sets of 125 contractions at supramaximal intensity, with a progressive regime of 2 to 5 times per week for 30 minutes a day, with an average of 10,000 muscle contractions per month for 3 years[37] **(C)**. The electrical stimulus is generated by a portable stimulator for home use, which contains the monitoring software to ensure its use[37] **(C)**. This type of electrically induced muscle contraction increases the mechanical load on the tibia (1.4 times body weight) of the treated limb. This is the possible effect related to the greater reduction in BMD loss in the posterior region of the tibia in the treated limb (2.6% per year), compared to both the non-treated limb (14.3% per year), and the anterior region of the tibia on the treated side (7.6%)[37] **(C)**.

An intensive program of electrical stimulation on the quadriceps muscle, for 1 hour, 5 times a week for 6 weeks, reduces the loss of local BMD in patients with complete SCI, up to 12 weeks post-injury[38] **(B)**. However, it is not known whether these benefits are maintained in the long term[38] **(B)**. And electrical stimulation on the quadriceps for 1 hour per day, 5 days a week for 24 weeks, significantly increases BMD of the distal femur and proximal tibia, but not the medial tibia ($p < 0.05$)[39] **(B)**. A recovery of close to 30% of the bone loss

was observed[39] **(B)**. It has also been documented that the benefit of electrical stimulation occurs only on the areas of stimulation, with a return to base values after discontinuation of stimulus treatment, and return to baseline within months, once stimulation is suspended[30] **(B)**.

An electrical stimulation protocol that induces knee extension in complete and incomplete tetraplegics, 3 times per week for 12 weeks for a total of 36 sessions, promotes progressive, continuous intensity up to the maximum load of 15 kg. There was no improvement in BMD of the tibia after treatment ($p > 0.05$), although values were better than those predicted in the study[40] **(B)**.

A protocol of electrical stimulation for 30 minutes a day, 5 days per week for 6 to 11 months does not alter BMD of the proximal tibia before and after training, in neither trained nor untrained limbs ($p > 0.05$)[41] **(B)**.

Ultra-sound

Therapeutic pulsed ultrasound applied to the heel of patients with spinal cord injury for 20 minutes a day, 5 times a week for a period of 6 consecutive weeks does not improve any parameter ($p > 0.05$). Therefore, for the near-term, ultrasound is not effective for the treatment of bone loss after SCI[42] **(B)**.

Recommendation

FES-cycle ergometer training mitigates the loss of bone mineral density in the stimulated areas of the treated limb such as the distal femur and tibia, during the acute period of the spinal cord injury, however these benefits are not maintained after three months[26-28] **(B)**. The use of FES in the chronic phase of SCI is still controversial[29-34] **(B)**.

Electrical stimulation of the quadriceps muscle for six weeks reduces the loss of BMD in the femur of patients with acute complete SCI, but it is not yet known whether these benefits continue in the long term[38] **(B)**.

Ultrasound, in the near term, is not effective for treating bone loss after spinal cord injury[42] **(B)**.

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