

Increased Bone Mineral Density after Prolonged Electrically Induced Cycle Training of Paralyzed Limbs in Spinal Cord Injured Man

T. Mohr,¹ J. Pødenphant,² F. Biering-Sørensen,² H. Galbo,¹ G. Thamsborg,² M. Kjær²

¹Department of Medical Physiology, Panum Institute, University of Copenhagen, Blegdamsvej 3, DK-2200 Copenhagen, Denmark

²Copenhagen Muscle Research Centre and Centre for Spinal Cord Injured, The Neuroscience Centre, National University Hospital, Denmark

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Abstract. Spinal cord injured (SCI) individuals have a substantial loss of bone mass in the lower limbs, equaling approximately 50% of normal values in the proximal tibia, and this has been associated with a high incidence of low impact fractures. To evaluate if this inactivity-associated condition in the SCI population can be reversed with prolonged physical training, ten SCI individuals [ages 35.3 ± 2.3 years (mean \pm standard error [SE]); post injury time: 12.5 ± 2.7 years, range 2–24 years; level of lesion: C6–Th4; weight: 78 ± 3.8 kg] performed 12 months of Functional Electrical Stimulated (FES) upright cycling for 30 min per day, 3 days per week, followed by six months with only one weekly training session. Bone mineral density (BMD) was determined before training and 12 and 18 months later. BMD was measured in the lumbar spine, the femoral neck, and the proximal tibia by dual energy absorptiometry (DEXA, Nordland XR 26 MK1). Before training, BMD was in the proximal tibia (52%), as well as in the femoral neck, lower in SCI subjects than in controls of same age ($P < 0.05$). BMD of the lumbar spine did not differ between groups ($P > 0.05$). After 12 months of training, the BMD of the proximal tibia had increased 10%, from 0.49 ± 0.04 to 0.54 ± 0.04 g/cm² ($P < 0.05$). After a further 6 months with reduced training, the BMD in the proximal tibia no longer differed from the BMD before training ($P > 0.05$). No changes were observed in the lumbar spine or in the femoral neck in response to FES cycle training. It is concluded that in SCI, the loss of bone mass in the proximal tibia can be partially reversed by regular long-term FES cycle exercise. However, one exercise session per week is insufficient to maintain this increase.

Key words: Spinal cord injury — Electric stimulation therapy — Bone density — Fractures — Exercise training.

Spinal cord injury (SCI) is known to result in a decrease in bone mass. This has been demonstrated in cross-sectional as well as in longitudinal studies, and in these studies the loss of bone mass was most pronounced in the lower limbs [1–3]. Whereas bone mass was found to be nearly unchanged in the lumbar spine, arms, and head, the bone mass in the proximal tibia decreased by 50% over the first 2 years postinjury [2, 3]. In addition to these findings, increased urinary calcium and hydroxyproline excretion during the

first 6 months following injury has indicated an accelerated bone resorption [4]. It is at present unknown if bone loss in the paralyzed lower extremities of SCI humans can be reversed by physical activity. This is of theoretical interest and, furthermore, of clinical relevance because previous studies have shown that in SCI subjects, inactivity-related bone loss is associated with an increased incidence of lower extremity fractures occurring upon only minor trauma [5–7]. With the use of electrical stimulation, SCI individuals can accomplish cycle training of their paralyzed legs, and we have now studied the effect of one-year intense training protocol (3 training sessions/week) on bone mineral density in the proximal tibia, the hip region, the lumbar spine, and the whole skeleton. Biochemical markers for bone formation and resorption in plasma and urine were also measured. In addition, during a 6 months follow-up period we investigated if a potential gain in bone mineral density could be maintained with less intense training (one session/week).

Materials and Methods

Ten SCI individuals [8 men and 2 women; mean age: 35 (range 27–45) years; mean weight 78.0 ± 3.8 (SE) kg] gave oral and written informed consent and participated in the training study that was approved by the Municipal Ethical Committee of Copenhagen. Subjects were studied on average 12.5 (2–24) years after injury and all were neurologically stable. Six were tetraplegic (injury level: C6) and four paraplegic (injury level: T4). They all had complete motor lesion in the lower extremities, and full passive hip and knee range of motion. The training program consisted of functional electrical stimulation of the legs for 30 min, three times a week for 12 months, followed by one time a week for 6 months. The training was performed on an upright seated computer-controlled functional electrical stimulation cycle ergometer (REGYS I Clinical Rehabilitation System, Tampa, FL) previously described in detail [8]. In short, dermal electrical stimulation of the quadriceps, hamstrings, and gluteal muscle groups was performed in sequence to cause pedaling of a work load adjustable cycle ergometer. The work load was as high as possible for all subjects throughout the study. Maximal oxygen uptake ($\text{VO}_2\text{-max}$) and power output were measured every third month to evaluate exercise induced changes in performance.

Bone mineral density (BMD) was measured in the lumbar spine (L2–L4), femoral neck, and proximal tibia with the subjects placed in the supine position using dual-energy absorptiometry (DEXA-scanner, Nordland XR 26 MK I, scan speed 60 mm/sec, line spacing 1.5 mm, point resolution 1.5 mm). Exposure to radiation was less than 1 μSv per scan [9]. Data from the lumbar spine and the femoral neck were compared with the normal range included in the scanner software program. Measurements on the proximal tibia were done using the so-called small animal program. The chosen

Table 1. The bone mineral density (BMD, g/cm²) (mean ± SE) in spinal cord injured subjects before (*n* = 10), after 12 months (*n* = 10), and 18 months (*n* = 9) of FES training^a

	Before	12 Months	18 Months
Femoral neck	0.63 ± 0.05+	0.61 ± 0.05+	0.55 ± 0.05+
Lumbar spine	1.21 ± 0.07	1.22 ± 0.07	1.23 ± 0.09
Proximal tibia	0.49 ± 0.04+	0.54 ± 0.04##+	0.48 ± 0.02+

^a The number of training sessions per week was reduced from three to one after 12 months of training

^b Difference (*P* < 0.05) from values before training

^c Difference (*P* < 0.05) from values in controls

area of interest was the proximal 7 centimeters of the tibia. Since no reference values existed for the BMD in the proximal tibia, five able bodied individuals (four males, one female), at similar ages, served as controls. Controls were studied twice with an interval of at least one week and the coefficient of variation between results in the same person was 2.3%. Serum and urine measurements were done at baseline and after 3, 6, 12, and 18 months. Serum osteocalcin was measured by a commercially available enzyme immunoassay with intra- and interassay coefficients of variation of 5% and 10%, respectively (Osteocalcin Elisa, DAKO, Copenhagen). Urine was sampled in the fasting state for measurements of deoxyypyridinoline by high performance liquid chromatography and was corrected for urine creatinine excretion. Intra- and interassay coefficients of variation were 6% and 13%, respectively [10]. Urinary creatinine was analyzed by Jaffe's chromogen reaction (Asstra, Beckman Instruments, Palo Alto, CA).

Statistical evaluation was done with the nonparametric Wilcoxon rank sum test. A level of 5% was considered significant (two-tailed testing).

Results

Prior to the training program, BMD in the proximal tibia (Table 1) was markedly lower (52%) in SCI subjects (0.49 ± 0.04 g/cm²) than in the control subjects (0.94 ± 0.03 g/cm²) (*P* < 0.05). As shown in Figure 1, low values for BMD were found especially in subjects who were studied a long time postinjury, BMD of the lumbar spine was not significantly different in SCI subjects as compared with able bodied subjects of the same age and sex, whereas femoral neck BMD was significantly reduced in the SCI subjects (Table 1).

After 12 months of training that was scheduled 3 times per week (mean number of sessions completed: 2.3 per week) the exercise capacity of the subjects had increased: they were able to perform exercise at a work load during pedaling between 1/8 Kp and 7/8 Kp, resulting in an oxygen uptake of 1.43 ± 0.09 liters/min (mean and SE) and an ergometer work output of 18 ± 2 KJ/session as compared with 1.20 ± 0.10 liters/min and 5 ± 2 KJ/session, respectively, in the start of the training period. During the 12 months of training, BMD of the proximal tibia rose significantly from 0.49 ± 0.04 g/cm² to 0.54 ± 0.04 , equivalent to an increase of $9.7 \pm 3.5\%$ (Fig. 2), whereas BMD of the lumbar spine and the femoral neck did not change significantly (Table 1).

Nine subjects performed six months of reduced training (one scheduled session per week, a mean of 0.9 completed per week). The oxygen uptake and work output decreased as compared to measurements at 12 months, to 1.26 ± 0.11 liters/min and 10 ± 2 KJ/session, respectively (*P* < 0.05). Also the BMD for the proximal tibia decreased, reaching a value (0.48 ± 0.02 g/cm²), which was not different from

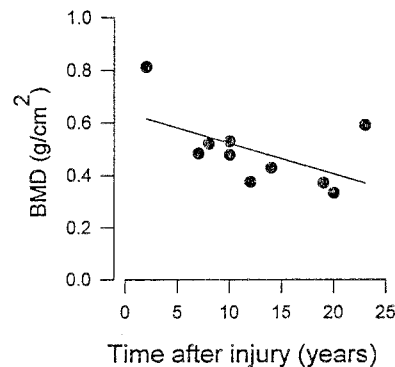


Fig. 1. Tibial bone mineral density (BMD) vs. time after injury in ten untrained spinal cord injured subjects. Regression line is drawn (*r* = 0.55, *P* < 0.10). In five age matched, able-bodied control subjects BMD was 0.94 ± 0.03 g/cm² (mean ± SE).

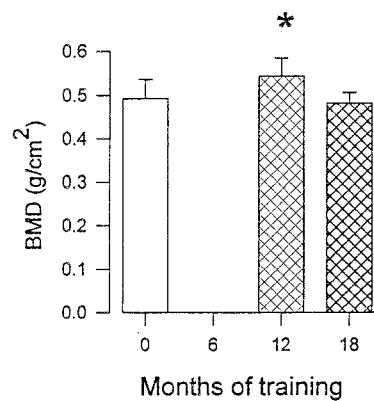


Fig. 2. Bone mineral density of the proximal tibia, measured in ten spinal cord injured subjects before FES training, after 12 months of training with three training bouts per week, and after an additional six months with reduced training, one training bout per week. Values are means and SE. * indicates value that is different from initial value (*P* < 0.05).

values prior to the training (*P* > 0.05; Fig. 2). Serum osteocalcin concentration and the urinary deoxyypyridinoline/creatinine ratio were within normal limits at baseline, and no significant changes were observed over time (*P* > 0.05; Table 2).

Discussion

The major finding of this study was the increased BMD of

Table 2. The serum osteocalcin and urinary deoxypyridinoline/creatinine (mean \pm SE) in spinal cord injured subjects before, after 12 months, and after 18 months of FES training^a

	Before training	12 Months	18 Months
Serum osteocalcin ($\mu\text{g/ml}$)	9.7 \pm 2.6 <i>n</i> = 10	8.8 \pm 1.7 <i>n</i> = 9	8.4 \pm 1.6 <i>n</i> = 8
Urinary deoxypyridinoline/creatinine ($\mu\text{mol/nmol}$)	24.1 \pm 9.1 <i>n</i> = 9	23.0 \pm 12.9 <i>n</i> = 8	18.8 \pm 8.6 <i>n</i> = 4

^a The number of training sessions per week was reduced from three to one after 12 months of training. Number of subjects (*n*) is given

the proximal tibia in response to electrically induced cycle training of paralyzed lower extremities in SCI individuals. Reversal of the bone loss seen in these patients has not been demonstrated.

We chose subjects who had sustained spinal cord injury more than two years before the study. Accordingly, they were all supposed to be in a new steady state for the bone mineral content in the proximal tibia, because it has been shown in a longitudinal study that bone mineral content (BMC) in the proximal tibia only decreases until a steady level at approximately 50% of the initial value is reached two years after injury [3]. However, in our patients the BMD in the proximal tibia before training tended to be inversely related to the time after injury, indicating continuous bone loss beyond the first two years postinjury (Fig. 1). This is in line with a cross-sectional study of 26 patients 2–25 years after spinal cord injury [1].

Because the BMD in the subjects studied would be expected to be stable or decreasing if no intervention had been made [1–3, 11], it is likely that the FES cycle training accounted for the observed increase in tibial BMD. This increase in BMD is interesting, because the reason for the high incidence of low-impact fractures in the legs of SCI individuals [5–7] probably is the fragility reflected in the subnormal BMD. In SCI individuals, the BMD below the pelvis has been estimated to be near fracture threshold [2]. No increase in BMD in the legs of SCI individuals has been demonstrated after use of passive standing (weight-bearing) in a standing frame or after use of various walking systems [12]. The effect of FES exercise on BMD in the tibiae of SCI individuals has to our knowledge only been studied by Hangartner et al. [11]. They studied a relatively newly injured population (mean of 6.4, range 0.1–22.4 years postinjury), and estimated a spontaneous decrease in BMD over time from pretraining measurements [11]. Compared with this, a lower than expected decrease in BMD was found after 14 weeks of training. The difference between expected and actually measured loss was most pronounced in the distal end of the tibia and in trabecular bone [11]. In the present study, after FES cycling, the increased BMD in the proximal tibia was not accompanied by any increase in BMD in other measured regions (Table 1). This is in accordance with other studies of SCI subjects undergoing a similar training program as in the present study [11, 13–15]. In one of those studies, 3 subjects were FES trained during 3 years, and no changes in BMD of the femoral head, femoral neck, or Wards triangle were seen [15]. The BMD values of the femoral neck were similar to ours [15]. The plasma concentration of osteocalcin reflects the level of ongoing bone formation whereas the urinary deoxypyridinoline/creatinine ratio reflects the level of ongoing bone resorption [16, 17]. Before training, these measures were within normal limits for able bodied individuals, corresponding to the

supposition that fractional bone turnover was fairly normal also. However, the increase in tibial BMD was not accompanied by changes in biochemical markers of bone turnover. The explanation is probably that the affected bone mass was too small to cause measurable systemic changes in bone markers. Studies of the influence of zero gravity, inactivity, and training in able bodied humans [18] have indicated that mechanical stimulation through pressure deformation and through tension development at muscle insertions enhance BMD. In the present study, electrically induced cycling was carried out against a resistance, which was small in absolute terms. However, the involved muscles were nearly maximally stimulated and, furthermore, the velocity of the tension rise during electrical stimulation was much higher than during voluntary contractions, and thereby might stimulate the bone formation more. Detectable changes in BMD only occurred in the proximal tibia, which is in line with the general views on the determinants of bone growth, since the proximal tibia is both the site of the insertion of the stimulated muscles and the site of direct transfer of the pedaling force.

The increase in BMD of the proximal tibia was seen after one year with training 2.3 times per week on average, whereas Hangartner et al. [11] investigated subjects after a mean of 14 weeks of training with 3 scheduled sessions per week. Bone responds slowly to stimuli that enhance growth. This may contribute to the fact that an absolute increase in BMD was seen in our study but not in the study by Hangartner et al. Our study indicates that a dose–response relationship exists between amount of training and the increase in proximal tibia BMD, since one training bout per week was not sufficient to maintain the elevated level of BMD achieved by training three times per week. It is not possible to tell if a further increase could have been obtained by higher amounts of training than applied in the present study, but in animals it has been shown that increasing training amounts to more than 3 times per week did not further increase BMD [19].

In conclusion, the present study has shown that the loss of bone mineral in the proximal tibia upon spinal cord injury can be partially reversed by FES exercise of the paralyzed lower limbs. The BMD increase found in the proximal tibia equals 10% in response to 3 training sessions of 30 min every week during one year. Since the SCI population is known to have a high risk of low impact fractures in their paralyzed lower limbs, which is associated with the reduced BMD close to the fracture threshold, the demonstrated training-induced increase is likely to have clinical significance. One training bout per week is apparently not sufficient to increase BMD. Finally, the study indicates that FES training has to be continued throughout life to maintain training-induced bone gains in SCI individuals.

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