Bone loss and bone turnover in acute and chronic spinal cord injured patients

Nurdan Paker, MD, PhD, Derya Bugdayci, MD, PhD, Sedef Ersoy, MD, PhD, Elif Uysal, MD, Sule Elbirlik, PhD.

ABSTRACT

Objectives: To investigate bone loss and the rate of bone turnover in individuals with spinal cord injury (SCI), and to compare the results with those healthy controls.

Methods: This cross-sectional, controlled study was performed between January and December 2005, in the Istanbul Physical Medicine and Rehabilitation Training Hospital, Istanbul, Turkey. Forty-eight patients with SCI were included in the study. The control group consisted of 47 age and sex matched healthy subjects. Bone density was measured at the proximal hip region by dual-energy X-ray absorptiometry. Serum levels of osteocalcin (OC) and C telopeptide of type 1 collagen (CTX) were measured.

Results: Femur neck and femur total bone mineral density values in the SCI patients and control group were 0.894 (0.188), 0.911 (0.185), and 0.994 (0.116), 1.063 (0.132) (p<0.03, p<0.000). Serum levels of OC and CTX were significantly increased in patients (p<0.015, p<0.000). Femur bone density in both neck and total regions showed a significant decrease in the SCI patients with longer injury duration (p<0.001, p<0.000). Serum CTX levels were markedly elevated in the first year of SCI. However, serum OC level showed no difference for the injury duration.

Conclusion: Significant bone loss was found at the proximal hip in SCI patients. Serum biochemical markers were also significantly higher in the patient group than the healthy controls. The bone density was lower in the long-standing SCI patients, although serum CTX levels were higher in the first 12 months after injury.

Neurosciences 2007; Vol. 12 (3): 232-235

From the Departments of Rehabilitation (Parker, Bugdayci, Ersoy, Uysal), and Biochemistry (Elbirlik), Istanbul Physical Medicine and Rehabilitation Training Hospital, Bahcelievler, Istanbul, Turkey.

Received 8th August 2006. Accepted 27th November 2006.

Address correspondence and reprint request to: Dr. Nurdan Paker, Department of Rehabilitation, Istanbul Physical Medicine and Rehabilitation Training Hospital, Bina ishani, No. 73/4 Nisantasi, Istanbul, Turkey. Tel. +90 (212) 2461538. Fax. +90 (212) 2465698. E-mail: nurdanpaker@hotmail.com

Bone loss occurs below the lesion level in spinal cord injury (SCI) patients.[1-4] Frey-Rindova et al[1] reported that bone mineral density (BMD) values at the radius and ulna did not decrease in paraplegic patients.[1] Osteopenia develops because of the decreased mechanical loading and following increased bone remodelling after paraplegia or tetraplegia.[5] Bruin et al[6] suggested that structural and geometrical changes of bone occurred after SCI. Bone loss due to SCI involves both cortical and trabecular bones. Trabecular bone loss occurs within the first 6 months after injury, but cortical bones are affected after the first year of injury and cortical osteopenia continues for a long time.[1,7] In a previous study,[8] trabecular bone loss at the knee in SCI women has shown to be more than postmenopausal women. Some investigators believe that bone density stabilizes 16-24 months after injury, although bone loss has shown to be continued long after injury in some studies.[6,9-11] Fractures can be prevented by determining the bone loss in patients with SCI. Significant osteopenia occurs especially at the lower extremities in paraplegia or tetraplegia.[10] This may be the reason fractures were seen frequently in the legs in SCI.[12] Biochemical bone markers of bone turnover are shown to reflect dynamic skeletal status and may help to identify increased bone loss and fracture risk.[13-16] Riis et al[14] concluded that fast bone turnover rate was as important as low bone mass for the risk of fracture in postmenopausal women. Zehnder et al[7] reported that bone resorption markers showed significant increases in SCI patients.[7] The elevation of bone formation markers are lower than resorption indicators in SCI.[17] The aim of our study was to evaluate bone density and biochemical bone markers in acute and chronic SCI patients and to compare the results with healthy controls.

Methods. This cross-sectional, controlled study was performed between January and December 2005, in the Istanbul Physical Medicine and Rehabilitation Training Hospital, Istanbul, Turkey. Forty-eight patients with SCI in the acute and chronic phase

were included in the study. All patients had traumatic SCI. Exclusion criteria included use of any medication with potential effect on the bone metabolism, having metabolic bone diseases, renal or hepatic diseases, heterotopic ossification and hyperthyroidism. Patients were divided in 2 subgroups according to the length of injury duration. Injury duration was less than one year in the first group and more than one year in the second group. The control group consisted of 47 age and sex matched healthy subjects.

Bone densitometry. Bone density measurement was performed by dual-energy X-ray absorptiometry (DXA) (Lunar model Dpx, Lunar Corp, Madison, WI) at the right proximal femur. The BMD values at the femur neck and proximal total femur were obtained. The BMD values at lumbar spine were not reliable because of spinal fusion material or vertebral fractures in the measurement site. For this reason, we did not measure the lumbar region. All measurements were carried out by the same experienced technician. Calibration of the DXA was checked by phantom scanning 3 times a week.

Biochemical bone markers. Fasting venous blood samples were taken between 8-9 am for analysis of osteocalcin (OC), C telopeptide of type 1 collagen (CTX), total alkaline phosphatase (ALP), calcium, phosphorus, and other routine biochemical tests. Serum intact OC and CTX were measured by micro enzyme-linked immunoabsorbent assay (ELISA). Laboratory reference ranges were 10-20 ng/ml for OC and 0.13-0.75 ng/ml for CTX.

Functional independence measurement (FIM). The FIM is used for evaluation of functional status in rehabilitation patients. It has motor and cognitive dimensions. In this investigation motor FIM scores were studied. Spasticity was evaluated with Ashworth Peterson scale. All the study subjects signed informed consent. This study was approved by the institutional ethical committee.

Statistical analysis was performed using SPSS version 13.5. Paired t test and Pearson Correlation test were used, and a $p<0.05$ was considered as statistically significant.

Results. Clinical and laboratory data are shown in Table 1. The level of the lesion was 18.75% cervical, 62.5% thoracic, and 18.75% lumbar. The length of injury duration was on average 24.52±20.9 months. The mean motor FIM score of the SCI patients was 35.18±20.9. Neurological deficit level was American Spinal Cord Injury Association (ASIA) grade AB in 26 patients and ASIA grade CD in 22 individuals. Thirty-nine patients were paraplegic and 9 were tetraplegic. Spasticity was observed in 33.3% of the patients. Biochemical bone

Table 1 - Clinical and laboratory data of the patients and control group.

Criteria	Patients	Controls	*P*-value
Number	48	47	-
Gender (Female/Male)	15 / 33	15 / 32	-
Age (year)	38.47±15.88	40.82±12.01	>0.05
Weight (kg)	71.02±21.45	75.34±11.79	>0.05
Height (cm)	166.39±20.79	167.10±9.31	>0.05
OC (ng/ml)	23.60±10.73	18.89±7.60	0.015
CTX (ng/ml)	1.37±0.60	0.62±0.25	0.000
Calcium (mg/dl)	8.87±0.57	9.05±0.43	>0.05
Phosphorus (mg/dl)	4.20±0.90	3.76±0.44	>0.05
ALP (U/L)	118.75±84.53	79.79±22.77	0.003

OC - Osteocalcin, CTX - C telopeptide type 1 collagen, ALP - Alkaline phosphatase

Table 2 - Clinical and laboratory data of the patients.

Parameters	Group 1	Group 2	*P*-value
Number	31	17	-
Length of injury duration (month)	4.35±1.67	61.29±88.04	-
OC (ng/ml)	24.69±12.01	21.61±7.85	>0.05
CTX (ng/ml)	1.50±0.65	1.12±0.39	0.017
Calcium (mg/dl)	8.87±0.60	8.86±0.52	>0.05
Phosphorus (mg/dl)	4.57±0.82	3.52±0.62	0.000
ALP (U/L)	130.96±101.54	96.47±29.01	>0.05

OC - Osteocalcin, CTX - C telopeptide type 1collagen, ALP - Alkaline phosphatase

Table 3 - Proximal femur bone mineral density values (BMD) and T scores of the study subjects.

Measurement sites	Group 1	Group 2	Controls
Femur neck BMD values(gr/cm²)	0.954±0.195	0.785±0.146	0.999±0.116
Total femur BMD values(gr/cm²)	0.992±0.182	0.762±0.136	1.063±0.132
Femur neck T scores	-0.766±1.46	-2.088±1.03	-0.408±0.8
Total femur T scores	-0.5±1.45	-2.258±1.09	- 0.094±1.02

Group 1 - Injury duration ≤one year
Group 2 - Injury duration >one year

markers, serum calcium, phosphorus, and alkaline phosphatase values of the 2 patient subgroups with injury duration of less than one year and more than one year are given in **Table 2**. The BMD values and T scores at the proximal hip were significantly lower in the patients with shorter and longer injury duration, compared to the control group (**Table 3**). Serum bone resorption markers were significantly higher in the patient group. There was a negative correlation between length of SCI and BMD values at femur neck ($p<0.01$), femur total ($p<0.02$), and T scores ($p<0.028$), (p 0.030). The FIM showed a positive correlation with the length of injury ($p<0.002$). There was a negative correlation between FIM and BMD values at femur neck ($p<0.005$) and femur total ($p<0.000$), and T scores at femur neck and total femur ($p<0.020$), ($p<0.000$). The BMD values at 2 measurement sites did not show any correlation with spasticity, age, height, weight, and ASIA grade.

Discussion. Our results showed bone loss at the 2 measurement sites of proximal hip and significant elevation of bone turnover markers in patients with SCI. Biering-Sorensen[11] suggested that bone loss affected primarily trabecular bones in the first year after injury. Bone mineral content at the femur neck and proximal tibia is reestablished 16-24 months after injury by development of an equilibrium between bone formation and resorption.[9,11] However, some investigators claimed that bone density did not stabilize within 3 years after SCI. Bruin et al[6] reported that significant trabecular and cortical bone loss, 35.3% and 12.9%, occurred 2 years after SCI. Osteopenia demonstrated a large variation between patients.[18] Szollar et al[19] did not find any bone loss at the hip by DXA measurement within the first 6 months after injury. They reported that osteopenia developed over longer periods.[19] In a previous study, bone loss was not observed at the lumbar spine or proximal hip in SCI patients 3 months after injury.[20] In our study group, osteopenia occurred within the first year after SCI. Early bone loss may be related to the exercise programs in which patients participated, different lifestyle habits like dietary calcium intake, and smoking.

Kıratlı et al[21] reported that BMD at the femur neck decreased 21% in the first year after injury. The BMD values at femur neck were 20% and 27% lower in the chronic SCI women and men than the controls. Maimoun et al[22] found a bone loss of approximately 22.5% at the total proximal femur, and 21.4% at the femur neck 71 weeks after injury. Wilmet et al[2] also reported 25% bone loss in the lower limbs at the end of the first year after injury. In this study, femur neck and proximal total femur bone density in the patients whose injury duration was less than one year was decreased by 4% and 6.7%. Bone loss was 22% for femur neck and 28% for femur total in the patients with 5-year injury duration. In the chronic SCI patients, T scores at the proximal total femur and femur neck region were 2 SD below the BMD values of healthy young adults in this study, whereas T scores at the proximal femur were in the normal range in the acute period. This means approximately 2 fold increase fracture risk at the proximal femur in the longstanding SCI patients. Szollar et al[23] found that BMD at the proximal femur decreased and reached fracture threshold 1-5 years after SCI.

In a previous study, almost 50% of the chronic SCI patients whose post injury period was more than 5 years, were shown above the fracture threshold in the femur.[24] Vestergaard et al[25] reported that low energy fractures were seen frequently in the lower extremities of patients with SCI. The fracture rate increased within 3 years after injury. Roberts et al[17] reported that bone resorption markers were elevated 10 fold above the normal value after acute SCI, although bone formation markers showed only a minimal rise in a 6 months duration longitudinal study. Bone resorption and formation markers did not differ between paraplegics and tetraplegics.[17] After the first year of injury, bone resorption has been shown to continue as represented by increased level of biochemical bone markers, whereas bone formation seems to be stabilised.[3]

In our study, the serum CTX level was significantly higher in both acute and chronic SCI. The CTX level was 2.4 fold of controls and the upper limit of reference range in the persons with injury duration of less than one year, and it was 1.8 fold of controls in the patients with 5-year injury duration. The rise of CTX was significantly higher in acute SCI. The serum OC values showed minimal elevation in both acute and chronic SCI.

Maimoun et al[22] suggested that bone resorption markers increased significantly 4 months after injury, although bone formation markers showed minimal elevation. In the patient group, 3 months after the injury, compared to controls, serum CTX level showed a 2.5 fold and serum OC showed a 1.6 fold increase in a previous study.[20] Total serum calcium level did not show any significant elevation in the patient group. Serum phosphate concentration was significantly higher in the patients with SCI post 3 months of the incident.[20] Blood calcium levels did not differ between spinal cord injured individuals and controls, although serum phosphate values showed significant elevation in patients one year after the injury in a previous study.[3] In this study serum calcium and phosphorus levels were in the reference range, although phosphorus was significantly higher within the first year of injury than the controls. Total ALP level was also elevated moderately in the SCI

patients, but it was within the reference range. In a previous study, higher total ALP levels were measured 9.5 months after SCI.[4] Some investigators reported that serum ALP level was in the reference range 3-4 months after injury.[3,20] Some authors suggested that spasticity had a positive effect on bone density.[4,24] In our study, spasticity had no positive effect on bone mass in the SCI individuals. There was no correlation between bone mineral content at the lower extremities and spasticity or flaccidity in a previous study.[2] Motor FIM scores showed a negative correlation with bone density at the proximal hip in this study. Dauty et al[3] suggested bone mineral content did not show significant differences between ASIA grade AB and grade CD patients.[3] Our results revealed BMD values at the proximal hip were similar in motor complete and incomplete individuals. In our study, BMD values at the proximal hip did not show a correlation with age, sex, weight, height, and ASIA grade.

In conclusion, we think that biochemical bone markers may be early predictors of bone loss in patients with SCI. If fast bone losers can be identified, future fractures could be reduced by early and effective rehabilitation programs, adequate dietery supplements of calcium and vitamin D or pharmacologic treatment with antiresorptive agents.

Acknowledgments. *We are grateful to all our colleagues in the clinic who have contributed to this study. I also would like to extend my special thanks to Dr. Muzaffer Tuzcu, who has edit-proofed the English text and to Dr. Rober Kasap for his contribution to prepare the Arabic text.*

References

1. Frey-Rindova P, Bruin ED, Stüssi E, Dambacher MA, Dietz V. Bone mineral density in upper and lower extremities during 12 months after spinal cord injury measured by peripheral quantitative computed tomography. ***Spinal Cord*** 2000; 38: 26-32.
2. Wilmet E, Ismail AA, Heilporn A, Welraeds D, Bergmann P. Longitudinal study of the bone mineral content and of soft tissue composition after spinal cord section. ***Paraplegia*** 1995; 23: 674-677.
3. Dauty M, Verbe BP, Maugars Y, Dubois C, Mathe JF. Supralesional and sublesional bone mineral density in spinal cord-injured patients. ***Bone*** 2000; 27: 305-309.
4. Demirel G, Yılmaz H, Paker N, Önel S. Osteoporosis after spinal cord injury. ***Spinal Cord*** 1998; 36: 822-825.
5. Kıratlı BJ. Immobilization Osteopenia. In: Marcus R, Feldman D, Kelsey J, editors. Osteoporosis. 2nd ed. San Diego (CA): Academic Press; 2001. p. 207-227.
6. Bruin ED, Vanwanseele B, Dambacher MA, Dietz V, Stüssi E. Long-term changes in the tibia and radius bone mineral density following spinal cord injury. ***Spinal Cord*** 2005; 43: 96-101.
7. Zehnder Y, Lüthi M, Michel D, Knecht H, Perrelet R, Neto I, et al. Long-term changes in bone metabolism, bone mineral density, quantitative ultrasound parameters, and fracture incidence after spinal cord injury: a cross-sectional observational study in 100 paraplegic men. ***Osteoporos Int*** 2004; 15: 180-189.
8. Slade JM, Bicket CS, Modlesky CM, Majumdar S, Dudley GA. Trabecular bone is more deteriorated in spinal cord injured versus estrogen-free postmenopausal women. ***Osteoporos Int*** 2005; 16: 263-272.
9. Chantrainne A, Nusgens B, Lapiere CM. Bone remodelling during the development of osteoporosis in paraplegia. ***Calcif Tissue Int*** 1986; 38: 323-327.
10. Garland DE, Stewart CA, Adkins RH, Hu SS, Rosen C, Liotta FJ, et al. Osteoporosis after spinal cord injury. ***J Orthop Res*** 1992; 10: 371-378.
11. Biering-Sorensen F, Bohr HH, Schaadt OP. Longitudinal study of bone mineral content in the lumbar spine, the forearm and the lower extremities after spinal cord injury. ***Eur J Clin Invest*** 1990; 20: 330-335.
12. Ragnarsson KT, Sell GH. Lower extremity fractures after spinal cord injury: a retrospective study. ***Arch Phys Med Rehabil*** 1981; 62: 418-423.
13. Delmas PD, Eastell R, Garnero P, Seibel MJ, Stepan J. The use of biochemical markers of bone turnover in osteoporosis. ***Osteoporos Int*** 2000; 11(Suppl 6): S2-S17.
14. Riis BJ, Hansen MA, Jensen AM, Overgaard K, Christiansen C. Low bone mass and fast rate of bone loss at menopause: equal risk factors for future fracture. A 15 year follow-up study. ***Bone*** 1996; 19: 9-12.
15. Garnero P, Sornay-Rendu E, Claustrat B, Delmas PD. Biochemical markers of bone turnover, endogenous hormones and the risk of fractures in postmenopausal women: the OFELY study. ***J Bone Miner Res*** 2000; 15: 1526-1536.
16. van Daele PLA, Seibel MJ, Burger H, Hofman A, Grobbee DE, van Leeuwen JPTM, et al. Case control analysis of bone resorption markers, disability, and hip fracture risk: The Rotterdam study. ***BMJ*** 1996; 312: 482-483.
17. Roberts D, Lee W, Cueno RC, Wittmann J, Ward G, Flatman R, et al. Longitudinal study of bone turnover after acute spinal cord injury. ***J Clin Endocrinol Metab*** 1998; 83: 415-422.
18. Bruin ED, Dietz V, Dambacher MA, Stüssi E. Longitudinal changes in bone in men with spinal cord injury. ***Clin Rehabil*** 2000; 14: 145-152.
19. Szollar SM, Martin EME, Parthemore JG, Sartoris DJ, Deftos LJ. Demineralization in tetraplegic and paraplegic man over time. ***Spinal Cord*** 1997; 35: 223-228.
20. Maimoun L, Couret D, Rossi M, Leroux JL, Ohanna F. Use of bone chemical markers with dual-energy X-ray absorptiometry for early determination of bone loss in persons with spinal cord injury. ***Metabolism*** 2002; 51: 958-963.
21. Kıratlı BJ, Smith AE, Naunberg T, Kallfelz CF, Perkash I. Bone mineral and geometric changes through the femur with immobilization due to spinal cord injury. ***J Rehabil Res Dev*** 2000; 37: 225-233.
22. Maimoun L, Couret I, Mariano-Goulart D, Dupuy AM, Micallef JP, Peruchon E, et al. Changes in osteoprotogerin /RANKL system, bone mineral density and bone biochemical markers in patients with recent spinal cord injury. ***Calcif Tissue Int*** 2005; 76: 404-411.
23. Szollar SM, Martin EME, Sartoris DJ, Parthemore JG, Deftos LJ. Bone mineral density and indexes of bone metabolism in spinal cord injury. ***Am J Phys Med Rehabil*** 1998; 77: 28-35.
24. Eser P, Frotzler A, Zehnder Y, Denoth J. Fracture threshold in the femur and tibia of people with spinal cord injury as determined by peripheral quantitative computed tomography. ***Arch Phys Med Rehabil*** 2005; 86: 498-504.
25. Vestergaard P, Krogh K, Rejnmark L, Mosekilde L. Fracture rates and risk factors for fractures in patients with spinal cord injury. ***Spinal Cord*** 1998; 36: 790-796.