Relationship Between Bone Mineral Density and Functional Parameters of Paraplegic Patients in Short-Term After Spinal Cord Injury

Omurilik Yaralanması Sonrası Kısa Dönemde Paraplejik Hastaların Kemik Mineral Yoğunluğu ile Fonksiyonel Parametreleri Arasındaki İlişki

Duygu Geler Külcü, Güliz Gönül*, Birkan Sonel Tur*, Yeşim Kurtaiş*, Özlem Küçük, Peyman Yalçın***

Yeditepe Üniversitesi Tıp Fakültesi Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, İstanbul
**Ankara Üniversitesi Tıp Fakültesi Fiziksel Tıp ve Rehabilitasyon, **Nükleer Tıp Anabilim Dalı, Ankara, Turkey*

Summary

Aim: To determine the relationship between bone mineralization and functional activity level of paraplegic patients in short-term after spinal cord injury (SCI).
Material and Methods: Thirty paraplegic patients and twentynine healthy controls were admitted to this study. Bone mineral density (BMD) and Z-scores, together with serum calcium, phosphorus, alkaline phosphatase, parathyroid hormone and 25-hydroxyvitamin-D levels, urinary calcium and deoxypyridinoline excretion were measured. All patients underwent a rehabilitation program including range of motion and progressive resistance exercises, upper body ergometry exercises, standing training with long leg orthosis, wheelchair ambulation or walking either by orthosis or walking aids five times/week during hospitalization.
Results: There was no difference between the groups regarding BMD values and Z-scores. Mean serum calcium and parathyroid hormone levels were lower (p=0.016 and p<0.001, respectively), serum phosphorus and alkaline phosphatase levels were higher (p<0.001 and p=0.049, respectively) in the paraplegics as compared to the controls. Positive correlations were found between the radius BMD values and total duration of upper body ergometry exercise (r=0.550, p=0.027) and wheelchair use (r=0.622, p=0.010) and also between the femur BMD values and total duration of therapeutic standing (r=0.351, p=0.039). There was an inverse relationship between the femur BMD values and total duration of immobilization (r= -0.404, p= 0.033).
Conclusion: Early rehabilitation interventions may prevent bone demineralization. Paraplegic patients should be followed and evaluated also in long term for the increased risk of osteoporosis. *(From the World of Osteoporosis 2008;14: 57-61)*
Key words: Spinal cord injury, bone mineral density, bone turn over markers, osteoporosis

Özet

Amaç: Paraplejik hastalarda fonksiyonel aktivite düzeyi ile kemik mineralizasyonu arasındaki ilişkiyi omurilik yaralanması sonrası kısa dönem içinde araştırmaktır.
Gereç ve Yöntem: Çalışmaya otuz paraplejik hasta ve yirmidokuz sağlıklı kontrol alındı. Kemik mineral yoğunluğu (KMY) ve Z-skorları ölçüldü. Serum kalsiyum, fosfor, alkalen fosfataz, paratiroid hormon ve 25-hydroksivitamin-D düzeyleri, idrar kalsiyum ve deoksipridinolin düzeyleri çalışıldı. Tüm hastalar yatışları süresince haftada beş kez eklem hareket açıklığı egzersizleri, progresif dirençli egzersizler, üst ekstremite ergometri egzersizleri, uzun bacak yürüme cihazıyla ayakta durma egzersizleri, tekerlekli sandalye ile ambulasyon eğitimi ve ortez veya yardımcı cihazla yürüme eğitimine alındı.
Bulgular: Kemik mineral yoğunluğu değerleri ve Z skorları açısından gruplar arasında fark yoktu. Paraplejik grupta kontrol grubuna göre ortalama serum kalsiyum ve paratiroid hormon düzeyleri düşük, (sırasıyla p=0.016 ve p<0.001), serum fosfor ve alkalin fosfataz düzeyleri yüksek (sırasıyla p<0.001 ve p=0.049) bulundu. Radius KMY değerleri ile üst ekstremite ergometri toplam egzersiz süresi (r=0.550, p=0.027) ve toplam tekerlekli sandalye kullanım süresi (r=0.622, p=0.010) arasında ve femur KMY değerleriyle terapötik ayakta durma toplam süresi (r=0.351, p=0.039) arasında ilişki saptandı. Femur KMY değerleri ile immobilizasyon toplam süresi arasında ise ters ilişki saptandı (r=-0.404, p=0.033).
Sonuç: Erken rehabilitasyon uygulamaları kemik deminerlizasyonunu önleyebilir. Paraplejik hastalar, artmış osteoporoz riski açısından uzun dönemde de takip edilmeli ve değerlendirilmelidirler. *(Osteoporoz Dünyasından 2008;14: 57-61)*
Anahtar kelimeler: Omurilik yaralanması, kemik mineral yoğunluğu, kemik döngüsü belirteçleri, osteoporoz

Address for Correspondence/Yazışma Adresi: Dr. Duygu Geler Külcü, Başıbüyük Mahallesi Erdemli Cad. Narcity. C2 Blok. No: 24 Maltepe, İstanbul, Turkey
Tel.: 0216 578 41 08 Gsm: 0505 857 51 78 E-mail: d_geler@yahoo.com.tr **Geliş Tarihi/Received:** 06.08.2008 **Kabul Tarihi/Accepted:** 22.10.2008

Introduction

It is known that bone demineralization and osteoporosis occur in patients with spinal cord injury (SCI), which may lead to pathological fractures (1).The acute treatment of patients with SCI has always focused on the injury itself, but there are complications which arise immediately after the injury. Bone loss as a consequence of SCI should not be of secondary concern. Bone demineralization occurs rapidly during the first months after injury and slowly continues up to two years before equilibrium between bone resorption and formation is restored (2,3). Many factors may affect bone mineral density (BMD) in spinal cord-injured patients such as age, sex, level of injury, time since injury, ambulatory status, and rehabilitative interventions (1).
Early intervention may be critical to prevent osteoporosis. In order to design the neccessary interventions, it may be useful to understand the relationship between bone demineralization and the patient's functional status in the early stages of SCI. The aim of this study has been to determine this possible short-term relationship by investigating BMD and bone turnover in paraplegic patients.

Material and Methods

Population
Paraplegic patients with traumatic SCI admitted to Physical Medicine and Rehabilitation Department at the Ankara University School of Medicine, were included in this cross-sectional study. In order to minimize the influence of hormonal factors, age limits observed for inclusion in the study were 18 to 60 years for males and 18 to 40 years for females. All female patients were premenopausal. A time limit of maximally 6 months post-injury was also imposed.
Patients with heterotropic ossification, venous thrombosis, reflex sympathetic dystrophy syndrome, history of fracture (other than vertebrae due to traumatic event), chronic osteomyelitis, malignancy, use of drugs and systemic diseases affecting bone metabolism were excluded. The control group was chosen from individuals who had no risk factors for osteoporosis.
Demographic details and neurological status of the patients were recorded. The neurological status was defined and classified according to the American Spinal Injury Association impairment classification (ASIA) (4). Duration of immobilization (months), duration of therapeutic standing with long leg orthosis (months), duration of wheel-chair use (months), duration of ambulation either by orthosis or walking aids (months) and duration of exercise by upper body ergometry (months) were recorded as the functional parameters.
This study was approved by the Medical Ethics Committee of the Ankara University. All participants signed an informed consent.

Methods

Bone mineral density
Bone mineral density and Z-scores were measured at the lumbar spine (L2-L4), femur neck and distal radius with dual energy X-ray bone densitometer (Norland XR-36; Norland Co., Madison, WI). Bone mineral density was expressed in absolute terms (g/cm^2) and the absolute BMD for each patient was expressed with the Z-score which is the comparison of the measured values with the mean BMD of age and sex matched healthy control group. In this study, Z-score was preferred since it represents the number of standard deviations that the measurement is above or below the age-matched mean BMD.
Biochemical markers and calcium homeostasis
Early morning, fasting blood was collected. Measurements were made of the serum levels of parathyroid hormone (PTH) (measured by immunolight 2000 chemiluminescence), calcitonin, osteocalcin (OC) (measured by RIA), 25 hydroxyvitamin D (measured by HPLC technique), calcium, phosphorus, and total alkaline phosphatase (tALP). Serum OC and serum tALP were the designated bone formation markers.
Twentyfour hour and early morning urine specimens were collected for the estimations of the clearance levels of calcium and deoxypyridinoline (measured by HPLC technique) which were taken as bone resorption markers.
Procedure
All patients underwent a rehabilitation program including range of motion and progressive resistance exercises, upper body ergometry exercises, standing training with long leg orthosis, wheelchair ambulation or walking either by orthosis or walking aids. The frequency of physical training was 5 times per week during hospitalization. Physical therapy programs were customized according to the needs of the patients and each patient was physically trained for at least 1 hour a day.
Data analysis
Statistical analyses were performed by using the statistical package SPSS version 9.0. The comparison of BMD values and Z-scores between the patient and the control groups was performed by Mann-Whitney U test. In the patient group, Pearson correlation coefficient was used to determine the correlation of the functional parameters and the BMD values. The acceptance for statistical significance was considered to be $p < 0.05$ for group comparisons and r-values were considered for correlation analyses.

Results

Patient characteristics
Thirty paraplegic patients were analyzed and compared with twentynine age matched controls. The mean age of patients was 35.3±11.2 years and the mean age of controls was 36.5±9.2 years. Fifteen patients had complete lesion

according to ASIA. The mean body mass index (BMI) values of the patient group and of the control group were 22.1±3.5 kg/m^2 and 23.0±4.2 kg/m^2 respectively. There was no significant difference between the groups regarding age and BMI. Demographic and functional properties and neurological status of the patients are shown in Table-1.

Table 1. Clinical and functional characteristics of patients with SCI

		mean±sd[a]	
Age		35.38±11.2	
Body mass index (kg/m^2)		22.1±3.5	
Time since injury (months)		3.98±1.9	
Immobilization duration (months)		1.25±0.47	
Therapeutic standing duration (months)		2.41±0.64 (n=24)	
Upper body ergometry exercise duration (months)		0.85±0.9 (n=30)	
Wheelchair ambulation duration (months)		2.60±0.64 (n=24)	
Walking ambulation duration (months)		1.65±0.5 (n=6)	
		n	%
Gender	Male	15	50
	Female	15	50
Neurological level	Thoracal	18	61.5
	Lumbar	12	38.5
ASIA[b]	Incomplete	14	46.2
	Complete	16	53.8
Spacticity	+	8	23.1
	-	22	76.9

a: standard deviation,
b: American Spinal Injury Association Impairement classification

Parameters of bone mineralization

The mean BMD values for each region of SCI and control groups are shown in Table-2. There was no significant difference between groups regarding BMD values and Z-scores of all regions ($p > 0.05$). The radius BMD values were 13% higher, the femur and the lumbar BMD values were 4.7% and 1.9% lower, respectively in patients compared to those of controls.

Parameters of biochemical markers and calcium homeostasis

Parameters of biochemical markers and parameters of calcium homeostasis and their reference ranges are presented in Table-2. The mean serum levels of calcium and PTH of the paraplegics were significantly lower ($p = 0.016$ and $p < 0.001$, respectively) than those of the controls but they did not exceeded the reference ranges. Mean serum phosphorus level was significantly higher ($p < 0.001$) in the paraplegics than in the controls and corresponded to the upper limit of the reference range. The mean serum levels for calcitonin and mean serum 25-hydroxyvitamin-D were not different between the two groups ($p > 0.05$).

As bone formation markers; the mean tALP level was above the upper limit of the reference range and was significantly higher ($p = 0.049$) in the paraplegics than in the controls whereas the mean serum OC levels of the two groups did not differ significantly ($p > 0.05$).

Although the bone resorption markers of patients indicated a slight increase as compared to those of controls, they remained within the reference ranges. There was no statistically significant difference between the two groups in terms of the bone resorption markers ($p > 0.05$).

Correlation of BMD with functional parameters

There was a negative correlation between the femurBMD values and the total duration of immobilization ($r = -0.404$, $p = 0.033$). Positive correlations were found bet-

Table 2. Bone mineral density and biochemical parameters of patient and control groups

	SCI group (Mean±SD)	Control group (Mean±SD)	p
Calcium (8.6-10.2mg/dl)	9.27±0.60	9.59±.64	**0.016**
Phosphorus (2.7-4.5 mg/dl)	4.15±0.56	3.55±.60	**0.000**
Alkalinephosphatase(35-104 UI/L)	119.16±63.79	83.24±31.61	**0.049**
PTH (8.0-76 pg/ml)	23.11±13.32	44.14±24.14	**0.000**
25OHD3 (10-50 µg/L)	17.60±8.65	19.57±9.78	0.604
Calcitonin (0-10 pg/ml)	8.34±6.26	6.20±3.34	0.308
Osteocalcin (4.0-24 µg/L)	12.20±6.62	11.89±6.26	0.992
Urinary calcium (80-320 mg/24h)	253.86±196.54	149.49±76.48	0.084
Urinary deoxypridinoline (8.0-45 pmol/µmolcreatinine)	27.36±24.01	22.65±18.33	0.751
Radius BMD (g/cm^2)	0.46±0.10	0.40±0.08	0.072
Radius Z score	0.79±1.69	1.50±1.60	0.260
Lumbar BMD (g/cm^2)	0.99±0.14	1.01±0.15	0.555
Lumbar Z score	-0.22±.1.30	-0.69±1.26	0.334
Femur BMD (g/cm^2)	0.81±0.87	0.85±1.43	0.219
Femur Z Score	0.08±0.43	0.89±0.15	0.360

ween the radius BMD values and the total duration of upper body ergometry exercises (r= 0.550, p= 0.027) and the total duration of wheel-chair use (r= 0.622, p= 0.010). The femur BMD values also positively correlated with the total duration of therapeutic standing (r= 0.351, p= 0.039).

Discussion

In this study, relationships between BMD and functional parameters have been investigated in the short-term after SCI in paraplegic patients. The results of this study have shown that the radius and the femur BMD levels are significantly correlated with the functional activity level in paraplegic patients.

No BMD difference was found between the two groups in this study. Recent studies, which evaluated BMD of the forearm, femur neck and the lumbar spine have presented conflicting results (5-7). Maimoun et al (8), observed no differences in the BMD of these three regions three months after injury and Roberts et al (9) reported no BMD variation in the femoral neck between 8 and 24 weeks after injury.The results of these studies were similar to the results of our study. These results suggest that the dual X-ray absorptiometry (DEXA) technique for BMD estimation may not show evidence of demineralization in the early stages of SCI. However, in some studies osteoporosis in sublesional areas has been shown shortly after SCI by using the DEXA technique (6,7).

Several reasons may explain our findings. We did not know the basal BMD values of the patients just after injury. These data were estimated from measurements in our control subjects. This might cause bias in estimating the real bone loss. Furthermore, we did not survey and consider the physical activity level before SCI which might affect premorbid BMD level as well as the post-injury BMD level.

An inverse relationship between the femur BMD values and the total duration of immobilization and a positive relationship between the femur BMD and the total duration of therapeutic standing have been found in this study. These results show the importance of early mobilization on bone mineralization in the early stages of SCI. Early passive verticalization of the patient, such as therapeutic standing, decreases the magnitude of demineralization (2,10). Gravity associated with vertical positioning of the bones, e.g. standing, provides a stimulus for bone mineralization by increasing the intramedullary fluid pressure (11,12).The increased intramedullary blood pressure has a positive effect on bone mineralization (12). The loss of physical function after SCI leads to the degradation of trabecular bone micro architecture. It is hypothesized that the magnitude of the loads imposed on bone dictates its mineralization and structural design (13). High frequency, low-magnitude stimulation, such as exerted by skeletal muscle contractions during standing or low level functional activity, may be the primary determinant of trabecular bone structure (14,15). Furthermore, weight loading stimulates the osteoblastic activity in the spine (16,17). Modlesky C et al (18) investigated trabecular bone micro architecture of the proximal tibia and the distal femur in men with SCI by using magnetic resonance imaging and found that they were markedly deteriorated. Although, loading associated with ambulation and normal physical function is suggested to be critical to maintain both the trabecular connectivity and bone mineral mass by several studies (16-18), there are some opposing results reporting that standing or walking by themselves do not improve BMD and do not prevent osteoporosis (3,19,20). Our results are also somewhat contradictory to each other, since there was a positive correlation between the femur BMD values and the total duration of therapeutic standing but not with the total duration of walking. The reason for this observation may be due to limited number of walking patients.

Positive correlations between the radius BMD values and the duration of wheelchair use and upper body ergometry exercise were found in the present study. This result shows the importance of muscle strengthening exercises on bone mineralization. Goemaere et al (21). reported that using wheelchair increases the forearm BMD in SCI patients. In healthy tennis players BMD of dominant extremities was found to be higher than those of normal population which is possibly related to the mechanical stress exerted to the upper extremity used in the sportive activity (22). Although radius BMD values were 13% higher than those of the controls, no significant difference was observed between the two groups in this study. This result was considered to be due to evaluation in the short-term and suggested that radius BMD values might increase in the long-term due to the influence of exercises as reported previously (21,22).

In the present study, calcium homeostasis was found to have deteriorated, but bone formation and bone resorption markers of the patients were not found to be different than those of the controls except for the elevated tALP levels. However, recent studies have demonstrated elevated resorption markers in the early stages of injury by assessing "modern" markers such as N-terminal cross-linked telopeptides of type I collagen (NTX), C-terminal cross-linked telopeptides of type I collagen (CTX), procollagen type I N propeptide (PINP) (9, 23-26). Possible reasons for the differences with our results may be due to the smaller sample size and particularly less specific markers used in this study as compared to those of recent studies.

Since bone mineralization in SCI is multifactorial, medication should be started soon after injury in addition to the rehabilitation interventions, to prevent bone demineralization. Bisphosphonates should be chosen for the treatment since these have been shown by several studies (27-29) to prevent bone loss in SCI. Bisphosphonates inhibit osteoclast recruitment and activity and reduce accelerated bone resorption in SCI (30). Pearson et al (29) have compared the effects of conventional rehabilitation programs with and without cyclic etidronate, and found that BMD loss was prevented in only those patients who had become ambulatory and had received etidronate.

In conclusion, functional status of the paraplegic patients in the early stages of SCI was found to be closely related to bone mineralization. Early rehabilitation interventions should have positive effect on preventing bone demineralization. Patients with SCI should be followed and evaluated also in the long term for the increased risk of osteoporosis.

References

1. Clasey JL, Janowiak AL, Gater D. Relationship between regional bone density measurements and the time since injury in adults with spinal cord injuries. Arch Phys Med Rehabil 2004;85:59-63.
2. Dauty M, Perrouin VB, Maugars Y, Dubois C, Mathe F. Suprelesional and sublesional bone mineral density in spinal cord-injured patients. Bone 2000;27:305-9.
3. Vlychou M, Papadaki PJ, Zavras GM, Vasiou K, Kelekis N, Malizos KN, et al. Paraplegia-related alterations of bone density in forearm and hip in Greek patients after spinal cord injury. Disabil and Rehab2003;25:324-30.
4. Maynard FM , Bracken MB, Creasey G, Ditunno JF, Donovan WH, Ducker TB, et al. International Standards for Neurological and Functional Classification of Spinal Cord Injury. Spinal Cord 1997;35:266-74.
5. Biering-Sorensen F, Bohr H, Schaadt O. Bone mineral content of the lumbar spine and lower extremities years after spinal cord lesion. Paraplegia 1988;26:293-301.
6. Garland DE, Stewart CA, Adkins RH, Hu SS, Rosen C, Liotta FJ, et al. Osteoporosis after spinal cord injury. J Orthop Res 1992;10:371-8.
7. 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;33:674-7.
8. Maimoun L, Couret I, Micallef JP, Peruchon E, Mariano-Goulart D, Rossi M, et al. Use of bone biochemical markers with dual-energy X-ray absorptiometry for early determination of boneloss in persons with spinal cord injury. Metabolism 2002;51:958-63.
9. Roberts D, Lee W, Cuneo RC, Wittmann J, Ward G, Flatman R, et al. Longitudinal Study of Bone Turnover after Acute Spinal Cord Injury. J Clin End Metab 1998;83:415-22.
10. Kaplan PE, Roden W, Gilbert E, Richards L, Goldschimidt JW. Reduction of hypercalciuria in tetraplegia after weight-bearing and strengthening exercises. Paraplegia 1981;19:289-93.
11. Turner CH. Site-specific skeletal effects of exercise: importance of interstitial fluid pressure. Bone 1999;24:161-2.
12. Chantraine A, Van Ouwenaller C, Hachen H, Schinas P. Intramedullary pressure and intraosseus phlebography in paraplegia. Paraplegia 1979;17:391-7.
13. Frost HM. Skeletal structural adaptations to mechanical usage Redefining Wolff's law: the bone modeling problem. Anat Rec 1990;226:111-8.
14. Rubin C, Turner AS, Mallinckrodt C, Jerome C, McLeod K, Bain S. Mechanical strain, induced noninvasively in the high-frequency domain, is anabolic to cancellous bone, but not cortical bone. Bone 2002;30:445-52.
15. Rubin C, Xu G, Judex S. The anabolic activity of bone tissue, supressed by disuse, is normalized by brief exposure to extremely low-magnitude mechanical stimuli. FASEB J 2001;15:2225-9.
16. Kunkel CF, Scremin AME, Eisenberg B, Garcia JF, Roberts S, Martinez S. Effects of standing on spacticity, contracture and osteoporosis in paralysed males. Arch Phys Rehab 1993;74:960-4.
17. Uebelhart D, Demiaux DB, Roth M, Chantraine A. Bone metabolism in spinal cord injured individuals and in others who have prolonged immobilization. A review. Paraplegia 1995;33:674-77.
18. Modlesky C, Majumdar S, Narasimham A, Dudley G. Trabecular bone microarchitecture is detoriated in men with spinal cord injury. J Bone Miner Res 2004;19:48-55.
19. Sabo D, Blaich S, Hohmann M, Loew M, Gerner HJ. Osteoporosis in patients with paralysis after spinal cord injury. Arch Orthop Trauma Surg 2001;121:75-8.
20. Chow YW, Inman C, Pollintine P, Sharp CA, Haddaway MJ, Masry WE, et al . Ultrasound bone mineral density and dual energy X-ray absorbtiometry in patients with spinal cord injury: a cross-sectional study. Spinal Cord 1996;34:736-41.
21. Goemaere S, Van Laere M, De Neve P, Kaufman JM. Bone mineral status in paraplegic patients who do or not perform standing. Osteoporos Int 1994;4:138-43.
22. Kannus P, Haapasalo H, Sievanen H, Oja P, Vuori I. The site-specific effects of long-term unilateral activity on bone mineral density and content. Bone1993; 15: 279-84.
23. Uebelhart D, Hartmann D, Vuagnat H, Castanier M, Hachen H-J, Chantraine A. Early modifications of biochemical markers of bone metabolism in spinal cord injury patients. A preliminary study. Scand J Rehab Med 1994;26:197-202.
24. Clark JM, Jelbart M, Rischbieth H, Strayer J, Chatterton B, Schultz C, et al. Physiological effects of lower extremity functional electrical stimulation in early spinal cord injury: lack of efficacy to prevent bone loss. Spinal Cord 2007;45:78-85.
25. Pietschmann P, Pils P, Woloszczuk W, Maerk R, Lessan D, Stipicic J. Increased serum osteocalcin levels in patients with paraplegia. Paraplegia 1992;30:204–9.
26. 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 20040;15:180-9.
27. Chappard D, Minaire P, Privat C, Berard E, Mendoza-Sarmiento J, Tournebise H, et al. Effects of tiludronate on bone loss in paraplegic patients. J Bone Miner Res 1995;10:112-8.
28. Nance PW, Schryvers O, Leslie W, Ludwig S, Krahn J, Uebelhart D. Intravenous pamidronate attenuates bone density loss after acute spinal cord injury. Arch Phys Med Rehabil 1999; 80:243-51.
29. Pearson EG, Nance PW, Leslie WD, Ludwig S. Cyclical etidronate: its effect on bone density in patients with acute spinal cord injury. Arch Phys Med Rehabil1997;78(3): 269-72.
30. Bauman WA, Wecht JM, Kirshblum S, Spungen AM, Morrison N, Cirnigliaro C, et al. Effect of pamidronate administration on bone in patients with acute spinal cord injury. J Rehabil Res Dev 2005;42:305-13.