BONE METABOLISM IN PATIENTS WITH SPINAL CORD INJURY

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SUMMARY

Osteoporosis is one of the complications of the spinal cord injury. Although enhancement of bone resorption after the injury has been demonstrated, increase of bone formation is controversial. In this study; 26 patients with spinal cord injury and 25 healthy volunteers were evaluated for the bone formation and resorption markers. Seventeen patients had paraplegia and nine patients had tetraplegia. American Spinal Injury Association (ASIA) score and functional independent measure (FIM) were used for the evaluation of the patients. Patients were divided into three groups according to ambulation level as bedridden, wheelchair dependent and walking with asistive devices. Total and ionized calcium, phosphorus, calcium excretion in 24-hour urine, urinary calcium/ creatinine ratio, alkaline phosphatase, parathormone, osteocalcine,C telopeptyde concentration were measured. Total and ionized calcium, parathormone and osteocalcine were found significantly lower in patients. Phosphorus, C telopeptyde, urinary calcium and calcium/ creatinine ratio were found significantly higher in patients compared to controls. Total calcium was lower in tetraplegic patients than paraplegic patients. Urinary calcium excretion and urinary calcium / creatinine ratio were found significantly higher in bedridden patients. Urinary calcium excretion was significantly higher in patients with ASIA score ≥50 and osteocalsine was higher in patients with ASIA score >50.

In conclusion, we suggested that bone metabolism is different in spinal cord injury patients, bone formation does not equivalent bone resorption and related with the patient's muscle strength and activity level.

Key Words: *Spinal cord injury, bone metabolism, osteoporoz.*

ÖZET

OMURİLİK HASARLI HASTALARDA KEMİK METABOLİZMASI

Medulla spinalis yaralanmasının komplikasyonlarından birisi de osteoporozdur. Yaralanma sonrası kemik yıkımında hızlı artış gösterilmesine rağmen, kemik yapımının hızı tartışmalıdır. Bu çalışmada 26 medulla spinalis yaralanmalı hasta ve 25 sağlıklı gönüllü, kemik yapım ve yıkım parametreleri bakımından değerlendirildi. 17 hasta paraplejik, 9 hasta ise tetraplejikti. American Spinal Injury Association (ASIA) skoru ve fonksiyonel bağımsızlık ölçümü (FIM) kullanıldı.. Hastalar yatak düzeyi, tekerlekli iskemle düzeyi ve yardımcı cihazla yürüme olmak üzere 3 gruba ayrıldı. Hasta ve kontrol grubunun serumunda total ve iyonize kalsiyum, fosfor, albumin, alkalen fosfataz, parathormon, osteokalsin ve C telopeptit düzeyleri, 24 saatlik idrar kalsiyum atılımı ve spot idrar kalsiyum/ kreatinin oranı ölçüldü. Total ve iyonize kalsiyum, parathormon ve osteokalsin düzeyleri, hasta grubunda kontrol grubuna göre istatiksel olarak anlamlı oranda düşük, fosfor, idrar kalsiyum atılımı ve spot idrar kalsiyum / kreatinin oranı ise yüksek bulundu. Total kalsiyum düzeyi tetraplejik hastalarda paraplejik hastalara göre daha düşüktü. 24-saatlik idrar kalsiyum atılımı ve spot idrar kalsiyum/ kreatinin oranı yatan hastalarda belirgin olarak yüksekti. 24 saatlik idrar kalsiyum atılımı ASIA skoru 50 nin altında olanlarda yüksek, osteokalsin ise düşüktü. Sonuç olarak, medulla spinalis yaralanmalı hastalarda kemik metabolizmasının farklı olduğu, kemik yapımının yıkıma eş oranda olmadığı ve kemik yapımının hastanın kas gücü ve aktivite düzeyiyle ilişkili olduğu düşünüldü.

Anahtar Kelimeler: *Medulla spinalis yaralanması, kemik metabolizması, osteoporoz.*

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INTRODUCTION

Osteoporosis is a common problem in patients with spinal cord injury. After injury accelerated bone resorption may lead to osteoporosis. Loss of biomechanical stress on the skeleton, neurovascular changes secondary due to autonomic nervous system disorders, structural changes of collagen and decreased levels of insulin like growth factor I have been attributed to the pathophysiologic mechanism underlying this condition (1).

Bone loss begins immediately after the spinal cord injury and goes on rapidly in the first year. Garland et al. (2) reported that one third of bone mineral has been lost within 3-4 months after the spinal cord injury. The rate of bone resorption increases two or three folds with respect to the normal subjects and causes not only an increment of fracture rate, but also a serious complication such as hypercalcemia, ectopic calcification and renal calculi (3).

Although the increased bone loss has been demonstrated clearly after spinal cord injuries, there is no consensus for the status of bone formation rate. While Pietschman (4) and Zanone (5) have reported increased bone formation rate, Uebelhart (6) suggested that bone formation rate was reduced.

Bone turnover is evaluated by the biochemical markers of bone formation (bone specific alkaline phosphatase, osteocalcine, procollagen type 1 and 3) and resorption (deoxsipyridinoline, pyridinoline, telopeptytes of type 1 collagen- CTx and NTx) (7). Although the specifities were low, total alkaline phosphatase has been used used for the evaluation of the bone formation and urinary calcium/ creatinine ratio for the bone resorption.

In this study, we assessed the bone formation and resorption rates by biochemical markers and evaluated the status of bone metabolism in patients with spinal cord injury.

MATERIAL AND METHOD

This study has a non-randomised and controlled design. Twenty-six patients with spinal cord injury and age matched twenty-five healthy volunteers were evaluated. They had no history of any systemic disease and they did not use any drugs interfering with bone metabolism. All women were at premenopausal period.

Age, sex, the duration of spinal cord injury, the injury of level, ambulation level and functional status was recorded. Patients were divided into the 3 groups according to injury level: cervical, thoracic and lomber. American Spinal Injury Association (ASIA 1992) score (8) was used for the motor evaluation and Functional Independence Measure (FIM)(9) was used for the evaluation of functional status. The patients were divided into two groups according to ASIA motor score (≥50 and >50) and FIM score (≥60 and >60) and further divided into three groups according to ambulation level as bedridden, wheelchair dependent and walking with assistive devices.

Morning fasting plasma and urine were collected in all patients and hepatic and renal function tests, alkaline phosphatase, calcium (Ca), phosphor (P), albumin, osteocalcine, parathormone (PTH), and eight patient's and all volunteer's C telopeptyde (CTx) were measured. Osteocalcine and PTH levels were measured by using radioimmunassay (RIA- Wallac Gama Counter), C telopeptyde level was measured by electrochemiluminescence (Elecsysis 2010, Roche Diagnostic) and ionised Ca level was measured by an ion selective electrode (AVL Analyzer) In addition, urine specimen for the 24 hours was collected for the determination of daily calcium excretion. The calcium exc-

retion > 250 mg was accepted as hypercalciuria. Urinary calcium- creatinine (Ca/Crea) ratio was measured in the early morning fasting urine specimen and the value of > 0.3 was accepted as a sign of high turnover rate.

Statistical analysis

Data were analysed using the SPSS for Windows program (Version 9.0; SPSS, Inc., Chicago, Illinois, USA) and expressed as means ± SD. The groups of homogenity of variance were calculated by Levene's test. ANOVA and student t test were used to compare the means of total Ca, ionized Ca, P, PTH, osteocalcine and betacross. Kruskal Wallis and Mann-Whitney U test were used to compare ALP, urinary Ca and Ca/ Cre ratio between the control, paraplegic and tetraplegic patients. Pearson correlation test was used for the correlation between the biochemical parameters. A value of $p<0.05$ was considered statistically significant.

RESULTS

Fifteen patients (57,7 %) were male, and eleven patients (42,3 %) were female. Control group included 11 (44 %) male and 14 (56 %) female. No differences were found in age and sex between the patient and control groups. The demographic variables were shown in Table I.

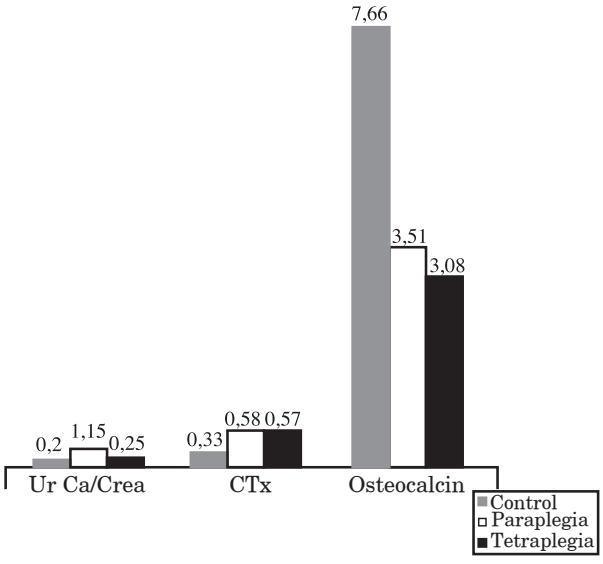
Seventeen (65,38 %) patients had paraplegia and nine patients (34,62 %) had tetraplegia. The injury level was cervical in 9 patients (34,62 %), at thoracic in 7 patients (26,92 %) and at lumbar level in 10 patients (38,46 %). Nine patients (34,62 %) were bedridden, twelve patients (46,15%) were wheelchair dependent and five patients (19,23 %) were walking with assistive device.

Tablo I: Characteristics of patients and control group

	Control	Paraplegia	Tetraplegia
N	25	17 (65%)	9 (35%)
Age (year)	38± 9	37± 9	35±11
Sex	14F,11M	7F,10M	4F, 5M
Duration (year)	-	6.45±5.34	3.5±6
ASIA motor	100	56.75±11.17	43±23.37
FIM	126	79±12.15	46±3.48

The values of total Ca and P were normal in the study group. Ionized Ca levels were lower than controls in four patients, but PTH levels were not high in these patients. Sixteen patients had hypercalciuria and twelve patients had high urinary Ca / creatinine ratio.

The mean values of biochemical parameters measured in the study and control groups, and differences between them were presented in Table II. Total and ionized calcium, PTH and osteocalcine were significantly lower and phosphorus, C telopeptyde, urinary Ca and calcium/creatinine ratio were significantly higher in patients than controls. There were no differences between paraplegic and tetraplegic patients in biochemical values except



Ur Ca/ Crea: Urinary Calcium/ Creatinine
CTx: C telopeptyde

Figure I: The bone metabolism markers in controls, paraplegic and tetraplegic patients

Table II: The mean values of biochemical parameters of the control and patients groups.

	Control	Paraplegia	Tetraplegia	p (C-P)	p (C-T)	p (P-T)
Total Ca (mg/dL)	8,98± 0,33	9,21± 0, 66	8,60± 0,58	0,059	0,000*	0,03*
Ionized Ca (mmol/L)	1,21 ± 0.06	1,14 ± 0.07	1,16 ± 0.08	0,003*	0.059	0,572
P (mg/dL)	3,53 ± 0,41	4,06 ± 0, 39	4,27 ± 0, 26	0,001*	0,000*	0,181
ALP (U/L)	184,7 ± 20,5	168,5± 44,6	121,7± 0,1	0,356	0,541*	1.000
Urine Ca (mg)	183,8 ± 68,7	288,2±139,5	259,5±119,3	0,000*	0,002*	0,744
Urine Ca/Cre (mg/dL)	0,2 ± 0,1	0,3± 0,1	0,2± 0, 001	0,023*	0,060	0,866
Osteocalsine (ng/ml)	7,72 ± 1,42	3,51 ± 2.07	3,18 ± 1,26	0,000*	0,000*	0,680
C telopeptyde (ng/mL)	0,34±0,09	0,49± 0,09	0,63± 0,12	0,013*	0,022*	0,154
PTH (pmol/L)	45,91 ± 8.9	41,72 ± 7.55	37.60 ±8.25	0,290	0,006*	0,390

C: Control; P: Paraplegia; T: Tetraplegia

* p< 0,05

total calcium (p=0.03). The differences in formation and resorption markers between the groups were presented as a graphic in the Figure I.

Age, sex and the duration of injury have no effect on bone metabolism. When the ambulation level is evaluated, urinary Ca excretion and urinary Ca / creatinine ratio were found higher in bedridden patients (p= 0.044; p= 0.029) Urinary Ca excretion was higher (p=0,037) in patients with ASIA score ≥50 and osteocalcine was higher in patients with ASIA score >50. When the functional status evaluated, ALP was found higher in patients with FIM score >60 (p=0,007).

There was a correlation between the ALP and osteocalcine (p:0,00, r:0,473), and urinary Ca- creatinine ratio and CTx (p= 0,00 r= 0.46). There was no correlation between total Ca and ionized Ca, urinary Ca, urinary Ca/ creatinine ratio, osteocalcine and PTH. Serum P level was correlated with urinary Ca/creatinine ratio (p= 0,022, r= 0,320), PTH (p= 0,024, r= –0,315), osteocalsine (p=0,00, r=-0,578) and CTx (p=0,031, r= 0,376). There was a positive correlation between osteocalsine and ALP, ionized Ca (p=0,00, r=0,508) and negative correlation between the osteocalsine and CTx (p=0,047, r=-0,349) and P (p=0,00, r= -0,578). Serum PTH level was correlated with P(p= 0,024, r= –0,315) and urinary Ca- creatinine ratio (p=0,038, r=-0,291).

DISCUSSION

In this study, twenty-six patients with spinal cord injury were evaluated for the bone metabolism. We found that while the markers of bone resorption were significantly higher, the markers of bone formation were significantly lower than control groups.

The increase of calcium excretion in 24-hour urine was the first sign of the bone resorption. Calcium excretion was increased within the first ten days and reached peak value in 4-6 month after the immobilization. (10). Naftchi et al. reported that hypercalciuria reached the peak values at seventh week and continued for 4 months and they did not found any differences between the paraplegic and tetraplegic patients (11). Also Claus Walker et al. (12) found that, hypercalciuria continued to the eight month after the injury and hypercalciuria was higher in patients with long term immobilization in bed. In our study group, urinary Ca excretion and urinary Ca / creatinine ratio were higher in patients with long term immobilization in bed and the results were consistent with the previous studies. Also the

patients with ASIA score ≥50 had higher level of urinary Ca excretion. These findings support the important effect of muscle strength on bone loss. The relationship between the duration of spinal cord injury and hypercalciuria was not found.

Hypercalcemia may be seen in patients with spinal cord injury as a result of increased bone resorption. It is frequently seen in young males with complete spinal cord injury, long-term immobilization in bed and cervical injury. Mynard (13) reported that the incidence of hypercalcemia was 11 % and all patients had tetraplegia. Vaziri (14) found that ionized Ca was normal and total Ca was lower, whereas other investigators (12,15) found them to be normal. Ionized calcium level and total calcium level was lower than control group in our study group and hypercalcemia was not found in any of the patients. Our study group is small and most of the patients had hypercalciuria. We thought that these findings may be related with the result of the calcium loss.

Serum P level is an important parameter for the Ca balance. Claus Walker (12), Vaziri (14) and Pietschman (4) found that phosphor level was normal in their study. Stewart (15) observed that P level was normal, but at its upper limit. P level was found a higher level according to control groups in our study group but we did not find any significant correlation between the total and ionized Ca and P, like the other studies (4,11,12).

Parathormone is a major hormone that affects the bone metabolism. Pietschman (4) showed that PTH was suppressed for 1-4 months and returned toward to normal range after the spinal cord injury. Roberts (1) followed these patients for six months and found PTH suppression during this period. Also Vaziri (14) reported that PTH was suppressed persistently for 3-5 years. In our study the PTH level was lower in tetraplegic patients than controls. But we did not follow up and we did not find any high level. But the number of the patients with tetraplegic is limited.

Pyridinoline, deoxypyridinoline, C telopeptyde (CTx) and N telopeptyde (NTx) are the new biochemical markers of bone resorption. Also urinary calcium / creatinine ratio may give information about the bone resorption with low sensitivity. Roberts (1) et al. suggested that all parameters rise at first week and reach peak values at 10-16. week and return to normal values at 6. months. There was no difference between paraplegic and tetraplegic patients with regard to deoxsypyridinoline and N telopeptyde levels, but pyridinoline was higher in tetraplegic patients. Uebelhart (6) found that bone resorption was increased using these parameters. Also Gencosmanoglu (16) reported that 77 % increase in urinary deoxsypyridinoline and 33 % in urinary N telopeptyde in patients with spinal cord injury. Pietschman (4) measured urinary Ca and creatinine ratio and found increased levels in spinal cord patients at two months and returning to the normal values at 6-12 months. Naftchi et al (11) suggested that the ratio is increased for 4 months and they did not found difference between paraplegic and tetraplegic patients. We found the increase of the urinary calcium creatinine ratio and CTx like the previous studies. But there was no difference between paraplegic and tetraplegic patients.. We did not find any significant effects of the duration, functional status and ASIA scores on bone resorption. We found that bone resorption was only related with the patient's ambulation level.

Bone specific alkaline phosphatase and osteocalcine are the specific markers of bone formation. However, a bone specific alkaline phosphate constitutes approximately 50% of total alkaline phosphates and in the absence of liver disease, total alkaline phosphates may reflect bone formation reasonably. Roberts (1) reported that bone formati-

on was lower than bone resorption in these patients and Uebelhart (6) suggested that bone formation was depressed. Pietscman (4) and Zanone (5) revealed that osteocalcine was increased progressively. We found lower osteocalcine levels in patients than control groups; we did not follow up the increase in osteocalsine level. But we did not find any high levels in patients with long-term spinal cord injury such as 6-12 months. When the activity level evaluated, we found that osteocalcine was significantly higher in ambulated patients than immobilized patients in bed. We suggested that bone formation is insufficient in these patients and related with ambulation level. But in our study group, the number of patients ambulated with orthoses was low.

In conclusion, bone resorption is increased dramatically, but bone formation is not increased in parallel with resorption. We suggest that bone metabolism is different in spinal cord injury patients. Bone formation was related with the patient's muscle strength and activity level. At the beginning of the injury, all patients are immobilized in bed, therefore bone resorption is increased. Then if the patients ambulate with the asistive devices, an increase in commence. But further studies are needed with large series and long-term follow up.

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