Longitudinal study of bone loss in chronic spinal cord injury patients

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Abstract. [Purpose] This prospective longitudinal study evaluated the changes in bone metabolism markers and bone mineral density of spinal cord injury patients over 3 years. We also assessed the relationships among the bone mineral density, bone metabolism, and clinical data of spinal cord injury patients. [Subjects and Methods] We assessed the clinical data (i.e., immobilization due to surgery, neurological status, neurological level, and extent of lesion) in 20 spinal cord injury patients. Bone mineral density, and hormonal and biochemical markers of the patients were measured at 0, 6, 12, and 36 months. [Results] Femoral neck T score decreased significantly at 36 months (p < 0.05). Among the hormonal markers, parathyroid hormone and vitamin D were significantly elevated, while bone turnover markers (i.e., deoxypyridinoline and osteocalcin) were significantly decreased at 12 and 36 months (p < 0.05). [Conclusion] Bone mineral density of the femoral neck decreases significantly during the long-term follow-up of patients with spinal cord injury due to osteoporosis. This could be due to changes in hormonal and bone turnover markers.

Key words: Bone loss, Spinal cord injury, Bone mineral density

INTRODUCTION

Osteoporosis is a well-known complication in patients with spinal cord injury (SCI). It is a serious complication that develops shortly after SCI, and its incidence peaks between 3 and 6 months3). Osteoporosis results in increased morbidity (e.g., pressure ulcers and spasticity/increased diaphoresis) and mortality owing to a 1–34% possibility of lower-limb fracture3). Therefore, it is vital to examine patients with SCI and initiate osteoporosis treatment before a fracture occurs.

Although immobilization secondary to SCI is considered the most important factor in osteoporosis, neural lesions (i.e., sympathetic and sensory denervation), circulatory disorders, and hormonal alterations (e.g., affecting parathyroid hormone, vitamin D, sex steroids, thyroid hormone, and leptin) are also implicated in the pathogenesis of osteoporosis2, 3). Thus, determining the risk factors for osteoporosis, educating high-risk groups to protect against the complications of osteoporosis, and providing necessary medical treatment will help decrease the mortality and morbidity due to osteoporosis and reduce treatment costs2, 4, 5).

Although numerous studies have investigated the presence of osteoporosis in SCI patients6–9), few longitudinal studies have examined bone mineral density (BMD) and bone turnover markers1, 9–11). Therefore, this prospective longitudinal study examined the changes in bone metabolism markers and BMD in patients with SCI over 3 years. This study was performed to determine the markers of bone turnover in order to identify SCI patients at risk of osteoporosis, because this is critical for prevention and treatment, as well as assess the relationships among BMD, bone metabolism, and clinical variables in SCI patients.

SUBJECTS AND METHODS

This was a prospective study of bone markers and BMD in patients with traumatic SCI. During 2006–2012, 20 subjects were recruited from the Physical Medicine and Rehabilitation Department, Ege University Medical Faculty, Turkey. Patients aged 18–65 years who had traumatic SCI with neurological involvement and provided informed consent to participate in the study were recruited. Patients with SCI without neurological involvement, non-traumatic SCI (e.g., metastasis, myeloma, vertebral infection, and vascular malformation), any other disease or receiving any medication that might affect bone metabolism were excluded.

The clinical data (immobilization because of surgery, neurological status, neurological level, and length of lesion) of the participating SCI patients were assessed at months 0, 6, 12 and 36 after the injury according to the following parameters:
The BMD of the lumbar spine (L1–L4 vertebrae), femoral neck, femoral total, and wrist was measured in g/cm² using dual-energy X-ray absorptiometry (DEXA) with a Hologic QDR 4500A scanner (Hologic, Waltham, MA, USA). In our laboratory, the coefficient of variation for BMD measurements was 1.0% for the lumbar spine, wrist, and femoral regions. BMD was measured according to the T score, which is the number of standard deviations above or below the mean in young adults. The DEXA results were examined by two nuclear medicine specialists.

In accordance with the World Health Organization criteria, osteoporosis and osteopenia were defined as T scores <2.5 SD and between −1 and −2.5 SD, respectively.

Whole blood counts as well as liver and renal function tests were performed concurrently. Moreover, blood specimens were analyzed for creatinine, creatinine clearance, serum calcium and phosphate, and 24-h urinary calcium and phosphate by using standard automated techniques. Gonadal status was assessed by measuring the levels of follicle-stimulating hormone, luteinizing hormone, and free testosterone. Serum osteocalcin (a marker of bone formation), follicle-stimulating hormone, luteinizing hormone, and free testosterone were measured with an immunometric assay (Immulite Analyzer, Metra Biosystems, DPC’s Technical Services Department, USA). Urine deoxypyridinoline, which is used to monitor type 1 collagen resorption, was measured using an chemiluminescent enzyme-labeled immunoassay (Immulite Analyzer). Samples were stored at −70 °C until analysis. Serum-intact parathyroid hormone (PTH) was measured with an immunoradiometric assay (IDS, UK). The intra- and inter-assay coefficients of variation were less than 10% for all biochemical assays.

This study was approved by the local ethics committee of our university, and written informed consent was obtained from all patients.

SPSS version 19.0 for Windows was used all statistical analyses. Baseline demographics and clinical characteristics were compared using Fischer’s exact test for continuous data and the χ² test for categorical data. The Wilcoxon test was used to test the differences in measurements made 0, 6, and 12 months after SCI. Patients were classified as osteoporotic, osteopenic, or normal according to the T scores obtained by the Spearman’s correlation test. The level of significance was set at p < 0.05.

RESULTS

Twenty patients (mean age: 66 ± 7.23 years) met the inclusion criteria and agreed to participate in the study. Fifteen patients attended all four follow-up visits at 0, 6, 12, and 36 months after SCI, while 5 patient attended only 3 visits (0, 6, and 12 months). Patient demographics and clinical characteristics are summarized in Table 1. The demographics and clinical indicators with regard to the diagnosis (paraplegia and quadriplegia) did not significantly differ between the two groups (p>0.05).

Femoral neck T score was significantly lower at 36 months than 0 months (p < 0.05). Wrist BMD could not be measured at 36 months. There were no significant differences in lumbar spine or wrist BMD, or the corresponding T scores (p > 0.05).

Hormonal markers, bone turnover markers, blood biochemical markers, and BMD (femoral neck, whole femur, lumbar spine, and wrist, and T scores) measured at 0, 6, 12, and 36 months are presented in Table 2. Among the hormonal markers, PTH and vitamin D were significantly higher at 12 and 36 months than 0 months (p < 0.05). In addition, osteocalcin and deoxypyridinoline levels decreased significantly after 0 months (p < 0.05). There were no significant changes in any blood biochemistry variable (p > 0.05).

When patients were grouped according to the T scores at 0 months, 3 patients (20%) had osteoporosis, 8 patients (53.3%) had osteopenia in the femoral neck, and the T scores of the remaining 4 patients (26.6%) were within the normal range. According to the T scores of the whole femur obtained at 0 months, 4 patients (26.6%) had osteoporosis, 8 (53.3%) had osteopenia, and 3 (20%) had normal BMD. According to the T scores of the L1–L4 region at 0 months, 2 patients (13.3%) had osteoporosis, 3 (20%) had osteopenia, and 9 (60%) had normal BMD. However, 2 patients (13.3%) were osteoporotic, 3 (20%) were osteopenic, and 10 (66.6%) had normal BMD at the wrist region.

Whole-femur BMD was significantly correlated with the American Spinal Injury Association (ASIA) score (r = 0.54, p < 0.05). Meanwhile, femoral neck BMD was negatively correlated with the time after SCI (r = −0.62, p < 0.05) and duration of immobilization (r = −0.69, p < 0.01). Similarly, whole-femur BMD was negatively correlated with time after SCI (r = −0.57, p < 0.05) and duration of immobilization (r = −0.62, p < 0.05).

Furthermore, PTH was significantly negatively correlated with BMD of the femoral neck (r = −0.56, p < 0.05) and the

Table 1. Demographic and clinical data of patients with spinal cord injury

| Age (years) median [range] | 40.20 [15–77] |
|---------------------------|--------------|
| Diagnosis                 |              |
| Paraplegia (n)            | 14           |
| Quadriplegia (n)          | 6            |
| Complete/incomplete (n)   | 4/16         |
| Neurological level (n)    |              |
| Cervical                  | 6            |
| Thoracic                  | 13           |
| Lumbar                    | 1            |
| American Spinal Injury Association score |            |
| A                         | 4            |
| B                         | 4            |
| C                         | 6            |
| D                         | 5            |
| E                         | 1            |
| Time after spinal cord injury (months, median [range]) | 15 [1–168] |
| Standing (hours/day)      | 0 [0–8]      |
| Smoking (present n, %)    | 1 (5)        |

Table 1. Demographic and clinical data of patients with spinal cord injury
whole femur ($r = -0.52$, $p < 0.05$). However, there was no correlation between the mean daily duration of verticalization and lumbar spine BMD ($p > 0.05$). In contrast, femoral neck BMD was significantly correlated with the duration of the initial bed rest period ($p < 0.05$).

**DISCUSSION**

In the present study, the femoral neck BMD of patients with SCI was significantly lower at the end of the 3rd year than that at baseline. This is probably associated with the changes of hormonal and bone turnover markers.

Few longitudinal studies have evaluated BMD in patients with SCI. A review of the relevant literature shows that the BMD of the lumbar spine in SCI patients is preserved owing to mechanical loading as a result of sitting in a wheelchair\(^{14}\), while the BMD of the distal femur decreased by 22%, 27%, and 32% at 3, 4, and 32 months, respectively\(^{15}\). Whether the BMD of the radius decreases with time is unclear\(^{16, 17}\). Other studies also demonstrate the most obvious demineralization occurs in the long bones of the lower limbs, especially the lower third of the femur and upper third of the tibia\(^{5, 6, 16}\) and the femoral neck to a lesser extent\(^{8, 19}\). Among the long bones, the femoral neck was evaluated for BMD; the observed demineralization decreased longitudinally.

Lazo et al. classified BMD at the femoral neck in SCI patients on the basis of the World Health Organization criteria and found that 61%, 19.5%, and 19.5% of their patients had osteoporosis, osteopenia, and normal BMD, respectively\(^{19}\). They conclude that BMD measurement at the femoral neck can be used to quantify fracture risk in SCI patients. Meanwhile, in the present study, 21.4%, 57.1%, and 21.4 of the patients had osteoporosis, osteopenia, and normal BMD at the femoral neck, respectively. Furthermore, significant changes in the BMD of the femoral neck were observed during the 3-year follow-up. Taken together with the fact that hip fractures due to falls increases the risks of mortality and morbidity, the results suggest patients with SCI should be monitored over the long term for osteoporosis, which may develop at the distal femur, and receive appropriate antosteoporotic treatment if necessary.

The bone remodeling unit appears to be controlled by osteocytes and old osteoblasts embedded in mineralized matrix. Microdamage of the calcified bone material induces osteocyte apoptosis, which in turn triggers a bone remodeling sequence. In addition, in SCI, the increased adiposity of

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**Table 2. BMD/T score, hormonal markers, bone turnover markers, and blood biochemistry 0, 6, 12, and 36 months after SCI**

| Median [range] | 0 months | 6 months | 12 months | 36 months |
|---------------|----------|----------|-----------|-----------|
| **BMD (BMD/T score)** |          |          |           |           |
| Whole femur BMD (g/cm\(^2\)) | 0.77 [0.54–1.06] | 0.74 [0.56–0.91] | 0.73 [0.57–1.04] | 0.70 [0.45–1.16] |
| Whole-femur T score | −1.75 [−3.3–0.7] | −1.95 [−3.2–0.9] | −2.05 [−3.9–0.8] | −1.89 [−5.64–0.84] |
| Femoral neck BMD (g/cm\(^2\)) | 0.69 [0.56–1.00] | 0.7 [0.52–0.83] | 0.68 [0.49–0.93] | 0.61 [0.20–1.04] |
| Femoral neck T score | −1.65 [−3.1–0.9] | −1.7 [−2.8–0.7] | −1.9 [−3.4–0.9] | −2.21 [−5.65–0.20]* |
| Lumbar spine BMD (g/cm\(^2\)) | 1.04 [0.76–2.71] | 1.05 [0.83–3.04] | 1.04 [−1.05–1.81] | 1.06 [0.83–2.72] |
| Lumbar spine T score | 0.1 [−3–6.8] | 0.75 [−2.4–18.2] | 0.35 [−2.5–6.5] | 0.15 [−2.5–1.93] |
| Wrist BMD (g/cm\(^2\)) | 0.58 [0.5–0.7] | 0.60 [0.54–6.53] | 0.6 [0.54–0.71] |          |
| Wrist T score | −1.2 [−3.2–0.3] | −0.75 [−2.7–0.8] | −1.2 [−2.6–1.3] |          |

**Hormonal markers**

|               | 0 months | 6 months | 12 months | 36 months |
|---------------|----------|----------|-----------|-----------|
| TSH (mUI/mL)  | 1.35 [0.24–12.98] | 1.61 [5–8] | 1.52 [0.61–16.74]* | 1.43 [1.03–4.76] |
| 25 OH Vitamin D | 35.25 [5–66] | 39.80 [19–67] | 60 [15–156]* | 52 [7–73]* |
| Free T3 (pg/mL) | 3.12 [1.90–3.94] | 3.03 [2.47–4.27] | 3.1 [2.09–4.44] | 2.9 [2.49–4.19] |
| Free T4 (pg/mL) | 0.96 [0.67–1.76] | 0.98 [0.64–1.30] | 1.27 [0.79–1.64] | 1.46 [1.18–1.78] |
| PTH (pg/mL)   | 26.06 [6.93–68.36] | 27.8 [17.57–89.26] | 41.89 [23.7–67.1] | 43.54 [23.3–131.7]* |
| FSH (mIU/mL)  | 4.92 [1.82–21.78] | 4.18 [1.7–14.69] | 6.11 [2.1–95] | 6.15 [4.8–14.3] |
| LH (mIU/mL)   | 4.85 [1.96–11.48] | 5.67 [1.29–13.18] | 6.06 [1.65–25] | 4.04 [0.53–3.27] |
| Free testosterone (pg/mL) | 10.10 [1–36] | 8.2 [1.4–22] | 9.85 [2.4–24] | 12 [1.3–18.2] |

**Blood biochemistry**

|                   | 0 months | 6 months | 12 months | 36 months |
|-------------------|----------|----------|-----------|-----------|
| Serum Ca (mg)     | 9.3 [8.3–10.6] | 9.3 [8.4–9.9] | 9.3 [9.2–10.2] | 9.3 [8.8–9.9] |
| Serum P (mg)      | 4.3 [3–5.5] | 3.9 [3.1–5.4] | 3.7 [2.9–4.9] | 3.6 [3–4.7] |
| Ca in 24 h urine (mg/dL) | 124.5 [30–760] | 130 [56–547] | 170 [7–538] | 135 [58–549] |
| Creatinine clearance (mL/min) | 91.50 [37–783] | 112 [79–210] | 101 [23–112] | 100 [20–110] |

**Bone markers**

|         | 0 months | 6 months | 12 months | 36 months |
|---------|----------|----------|-----------|-----------|
| Bone ALP (U/L) | 21 [10–39] | 24 [7–31] | 23 [19–28] | 22 [18–26] |
| Deoxypyridinoline (nM/mmol) | 15.43 [6.67–38.24] | 9.93 [7.08–30.57]* | 8.6 [1.4–18.9]* | 5.72 [4.33–15.38]* |
| Osteocalcin (ng/mL) | 16.80 [2.7–46.9] | 13.10 [2.2–59.3] | 10.05 [2.45–8.8] | 4.86 [2.38–12.20]* |

BMD: bone mineral density, SCI: spinal cord injury, TSH: thyroid-stimulating hormone, PTH: parathyroid hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, ALP: alkaline phosphatase. *$p < 0.05$
the bone marrow impairs osteoblast differentiation\(^\text{20}\). Osteoblastic cells affected in this way negatively impact bone turnover. This could be responsible for the decreased bone turnover observed in our patients with chronic SCI. This could also be associated with changes in other hormones such as growth hormone or a decrease in IGF-1, which may result in reduced bone turnover; however, this was not dealt with in the present study\(^\text{21}\), and larger studies are required to evaluate this. Charmant et al. also found that bone metabolism started to decrease 12 months after injury but was never completely resolved\(^\text{22}\). Although some studies report hydroxyprolin return to baseline after SCI\(^\text{23, 24}\) as was observed in the present study, other studies report ongoing high bone resorption for up to 3–5 years. Moreover, studies investigating bone formation markers indicate different rates of variation of bone formation markers; bone formation markers range widely from low to high or no change\(^\text{18, 25}\). The assessment of bone turnover may reflect ongoing bone remodeling more accurately than bone mass measurements. Therefore, the assessment of bone turnover in SCI patients in both the acute and chronic stages is important not only for determining which individuals are at risk of osteoporosis, but also planning prophylactic measures against osteoporosis. Therefore, additional studies investigating bone metabolism at more frequent intervals in larger sample sizes are required to investigate this in detail.

After acute SCI, the PTH-vitamin D axis is suppressed, with depressed PTH and 1,25 (OH) vitamin D levels. However, a reversal in parathyroid activity from 1–9 years after injury has been noted. Moreover, secondary hyperparathyroidism is thought to accelerate the development of SCI-induced osteoporosis\(^\text{21}\). Among the studies investigating the reason for osteoporosis in patients with SCI on the basis of this information, some studies report mild secondary hyperparathyroidism in chronic SCI\(^\text{26}\), while others report that PTH does not change\(^\text{26}\) or decreases\(^\text{27}\). Findings regarding vitamin D metabolism in chronic SCI patients are even less consistent. Bauman et al. report increased vitamin D levels in patients with chronic SCI\(^\text{26}\); they suggest this is because elevation of the absolute serum PTH level in some SCI patients might have resulted in significantly higher vitamin D levels. However, they found vitamin D levels were low in chronic SCI patients in another cross-sectional study\(^\text{27}\). Possible reasons for these discrepancies among studies include ethnic differences, diet, and sun exposure. Similar to the study conducted by Bauman et al.\(^\text{26}\), PTH and vitamin D levels were high in the patients with chronic SCI in the present study.

Several factors may influence bone loss after SCI. We found that, similar to Dauty et al.\(^\text{20}\) the degree of demineralization at the lumbar spine, lower limbs, and radius was independent of the neurological level. We also found that the loss of bone mass increased with the duration of acute post-traumatic immobilization and time after injury. Although the relationship between ASIA scores and femoral BMD in SCI patients reflects the relationship between mobility and BMD, the present study corroborates the lack of an effect of weight bearing between verticalization and BMD. Other studies also demonstrate the lack of a preventive effect of verticalization on bone mineralization regardless of duration or frequency\(^\text{3, 6, 8}\). Nevertheless early verticalization is still recommended to alleviate the deleterious effects of bed rest on the lower limbs. Moreover, pharmacological therapy in addition to physical activity such as standing upright appears to be necessary to prevent bone loss in SCI patients\(^\text{26}\). On the other hand, it should be noted that fracture risk can increase during therapy; therefore, aggressive lower-limb muscle strengthening exercises should be avoided. No other correlations were detected between indexes of bone metabolism and bone density measurements. This lack of correlation could be a phenomenon similar to the loss of interaction between the neurohypophysis and serum fluid electrolyte balance observed after SCI\(^\text{28}\).

Very few long-term longitudinal studies of bone health have been performed in patients with SCI. In most previous longitudinal studies, SCI patients were monitored for osteoporosis for 5 weeks to 3 months following the acute period (approximately 3 months)\(^\text{9, 10, 29}\). Increases in bone formation markers from normal to clearly elevated levels and a gradual increase in bone destruction markers were observed in SCI patients during the acute period\(^\text{9, 10}\). Furthermore, rapid onset of bone loss was detected following SCI\(^\text{29}\). Bruin et al. performed tibial peripheral quantitative computed tomography scans on 12 SCI patients and evaluated quantitative bone loss for 2 years following the acute phase (week 5); decreases in the trabecular, cortical, and geometric characteristics of the tibia were observed\(^\text{30}\). Meanwhile, Sorensen et al. monitored SCI patients for a median period of 41 months starting from approximately day 43 after injury; they observed that BMD in the lower extremities decreased after injury and a new steady state level was reached 2 years post-injury in the femoral neck at 60–70% of normal levels\(^\text{7}\). In the present study, SCI patients were admitted 15 months after injury and monitored for 3 years, and changes in both BMD, and hormonal and biochemical markers were observed in the chronic period. The fact that SCI patients were monitored after the acute period can be considered a limitation of this study. However, it also has important advantages over other longitudinal prospective studies, such as providing long-term monitoring, elucidating the changes during the chronic period, and allowing all aspects of bone loss (i.e., BMD, and hormonal and biochemical markers) to be examined. Studying the trends of BMD and bone turnover markers in a longitudinal study would be useful. However, the referral of patients to rehabilitation is unfortunately delayed in our country, with SCI patients being referred to rehabilitation centers an average of 1 year after injury. Performing longitudinal and prospective studies, enrolling SCI patients during the acute phase, and measuring BMD and bone turnover markers would greatly contribute to the existing knowledge base of SCI.

Although the absolute number of patients in the present study was low, it is relatively higher than that of other longitudinal studies of SCI\(^\text{9, 10}\). Nevertheless, the numbers of complete/incomplete SCI and paraplegic/quadruplegic patients were insufficient, precluding statistical analyses of these patients. SCI patients have a greatly increased risk of fracture, but no prospective studies have examined the onset of fracture in such patients.

In conclusion, a 3-year follow-up of SCI patients referred
to rehabilitation approximately 1 year after injury revealed a significant decrease in the femoral neck T score at 3 years. In addition, bone turnover markers were low. This study is the first to demonstrate bone loss continues in the chronic phase after SCI. Our study suggests the importance of physical mobility in SCI patients; however, further studies are required to confirm this.

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