Changes of basic bone turnover parameters in short-term and long-term patients with spinal cord injury

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Abstract The bone mineral density (BMD), the cross- links (PYD, DPD and NTx) and the bone specific alkaline phosphatase (BAP) was investigated in a cross-sectional study in 62 male patients with spinal cord injury (SCI), $n = 28$ short-term (0–1 year after SCI) and $n = 34$ long-term SCI patients (> 5 years after SCI). Knowledge about this parameters are necessary to find an adequate therapy for this special kind of osteoporosis. Immobilisation osteoporosis in SCI patients is a well-known problem that may lead to pathological fractures. Little is known regarding the extend of the osteoporosis as well as the causative factors. Measurements of the BMD in the proximal femur and the lumbar spine were performed with dual-energy-X-ray-absorptiometry (DEXA), of the osteoblast marker BAP (bone specific alkaline phosphatase) from serum and the osteoclast markers PYD (pyridinoline), DPD (desoxy-pyridinoline) and NTx (N-telopeptide of collagen type I) from urine. We found a significant decrease of BMD in the proximal femur and no relevant change in the lumbar spine compared to an age- and sex correlated control group (Z-score) in

short-term and long-term SCI patients. There was a significant bone loss at the proximal femur between short and long-term SCI patients, whereas at the lumbar spine the BMD even slightly increases. Bone resorption (cross-links) was increased in both groups, though in long-term SCI patients it is significantly decreased compared to short-term SCI patients (DPD from 211.7 u/g creatinine to 118.1 u/g creatinine; NTx from 215.1 nmol/mmol creatinine to 83,6 nmol/mmol creatinine). The bone formation marker BAP is slightly below normal range in both groups (12.3 U/l in short-term, 9.7 U/l in long-term SCI patients). Only the proximal femur is affected by the immobilisation osteoporosis of SCI patients, therefore the BMD measurements in these patients should be performed at the lower limb. The problem of the immobilisation osteoporosis in SCI patients is the striking increase of bone resorption and the missing reaction of the bone formation.

Keywords Immobilisation-osteoporosis · Spinal cord injury · Paraplegia · BMD · Cross-links · Bone formation · Bone resorption

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Introduction

Osteoporosis in spinal cord injury (SCI) patients has been a well known problem for a long time. According to literature about 11% [4] of the patients get pathological fractures. Typical for these pathological fractures is the so called “paraplegic fracture”—a supracondylar fracture of the distal femur caused by inadequate trauma; e.g. by transfer from wheelchair to bed [4, 7].

In the last few years some studies have been published about the changes of bone mineral density (BMD) after SCI [1, 5, 8, 12, 15, 17]. They show that especially the nonloaded regions of the body (e.g. hip or tibia) are affected by immobilisation osteoporosis after SCI.

It has been possible to show the activity of the osteoclasts with the so called cross-links PYD (pyridinoline), DPD (desoxypyridinoline) and NTx (N-telopeptide of collagen type I) and those of the osteoblasts with the bone specific alkaline phosphatase (BAP) for some years. But there are only few studies about the change of these bone markers after SCI [5, 17], and only one “cross-link”—the DPD (desoxypyridinoline)—is examined. Some authors maintain the NTx as a more specific marker than PYD or DPD [14]. Knowledge about the changes of bone markers in SCI patients is essential for the understanding of the SCI specific immobilisation osteoporosis and its therapy.

The aim of this study is to investigate the changes of the bone mineral density, the cross-links PYD, DPD and NTx and the BAP—which are the basic parameters to describe bone turnover after SCI—and so to learn more about this type of osteoporosis and its possible therapy.

Materials and methods

The BMD at the lumbar spine and the proximal femur was measured by dual-energy-X-ray-absorbiometry (DEXA, QDR 2000 Hologic). To exclude the influence of the gender on the bone turnover parameters we examined only male patients treated at our hospital between January and December 1997.

A routine blood sample was drawn to exclude other bone turnover relevant diseases, including the erythrocyte sedimentation rate, differential blood count, alkaline phosphatase, urea, creatinine, total protein assay, sodium, potassium, calcium and phosphate. Exclusion criteria were the use of drugs or diseases affecting bone metabolism or pathological results of the routine blood sample.

The bone alkaline phosphatase (BAP) was analysed from blood serum with an enzyme immuno-assay (Metra Biosystems Inc.). The measurement of the cross-links (connectors of collagen type I) was done from a urine specimen taken between 10 a.m. and 1 p.m. and immediately frozen afterwards.

Pyridinoline and desoxy-pyridinoline were determined by high-pressure liquid chromatography (HPLC-procedure). The HPLC-procedure is the so

called “gold standard” to analyse the DPD [13]. The NTx was determined by enzyme immunoassay (Ostex International Inc.).

The BMD was measured in $n = 62$ male patients with traumatic SCI. In $n = 24$ of these patients the blood sample and urine specimen to investigate the cross-links and the BAP were taken additionally.

We divided the patients into two groups: the short-term SCI patients (average age 36.3 ± 17.6 years) with SCI up to 1 year, and the long-term SCI patients (average age 35.9 ± 9.8 years) with SCI longer than 5 years. We examined $n = 28$ (15) short-term SCI patients and $n = 34$ (9) long-term SCI patients. The numbers in brackets relate to the patients with the additional analysis of the blood sample and urine specimen, the numbers without brackets relate to all patients.

The average age was 36.2 ± 14.0 (37.3 ± 15.9) years. The average time after SCI was 9.1 ± 10.9 (6.4 ± 9.2) years. The average body mass index (BMI) was 22.4 ± 3.9 (22.0 ± 3.8) kg/m².

$n = 30$ (11) of the patients are tetraplegics, $n = 32$ (13) are paraplegics, $n = 39$ (12) are stage A of Frankel, $n = 23$ (12) are stage B/C/D.

Statistics

The results are expressed as mean and standard deviation. Normal distribution was tested with the Kolmogorov Smirnov test. The results of the DEXA measurements were all within normal distribution, so we used the *t*-test. There was no normal distribution in all cases in the blood and urine tests. To compare the results of the blood and urine test we used the non-parametric Mann–Whitney *U*-test. A $p < 0.05$ was accepted as significant.

Results

The BMD of the short-term SCI patients' proximal femora (ROI Total) is 0.889 ± 0.169 g/cm², the *Z*-score (standard deviation of an age- and sex correlated control group) is slightly lowered with -0.658 ± 1.316 .

The BMD of the long-term SCI patients' proximal femora is significantly decreased to 0.633 ± 0.188 g/cm². The *Z*-score is with -2.773 ± 1.786 clearly decreased (Fig. 1, Table 1).

In the lumbar spine (L1–L4) the BMD doesn't decrease, it even slightly increases significantly between both groups. The BMD of the short-term SCI patients is 0.978 ± 0.163 g/cm², the BMD of the long-term SCI patients 1.094 ± 0.200 g/cm². But there is no significant difference ($P > 0.05$) between the *Z*-scores of both

Fig. 1 Z-score of the BMD at the proximal femur (ROI TOTAL) in short-term (0–1 year) and in long-term SCI patients (>5 years); significant decrease

Fig. 2 Z-Score of the BMD at the lumbar spine (L1–L4) in short-term (0–1 year) and in long-term SCI patients (>5 years); no significant change of the Z-score

groups (short-term SCI patients -0.315 ± 1.577 , long-term SCI patients 0.008 ± 1.919) (Fig. 2, Table 2).

Comparing paraplegic and tetraplegic patients, we could not find any significant difference in the BMD of the proximal femur or the lumbar spine, neither in short-term nor in long-term SCI patients (Table 3).

The BAP is reduced in short-term SCI patients (12.29 ± 15.24 U/l) and long-term SCI patients (9.67 ± 4.19 U/l) (Fig. 3). There is no significant difference between both groups.

All cross-links examined (PYD, DPD, NTx) are clearly increased in both groups (Fig. 4, Figs. 5, 6). The concentration of the cross-links in the urine of the long-term SCI patients decreases significantly compared to those of the short-term SCI patients, though it is still increased compared to the non-paraplegic controls.

Discussion

The BMD of the proximal femur of the long-term SCI patients is significantly decreased compared to the BMD of the short-term SCI patients. In long-term SCI patients there is a clear osteoporosis with a Z-Score

of -2.773 . The BMD of the lumbar spine of the short- and long-term SCI patients is within the normal range of the age- and sex correlated non-paraplegic population. This confirms the findings of the so called “dissociated hip and spine demineralisation” in patients after spinal cord injury [8, 10, 12, 17]. This explains the occurrence of osteoporotic fractures mainly at the lower limb of these patients and the absence of osteoporotic fractures of the upper limb that SCI patients in contrast to patients with an idiopathic osteoporosis nearly never suffer.

The mechanical stimulus on the vertebral body—e.g. by sitting in a wheelchair—probably stimulates the activity of the osteoblasts sufficiently, while the lower extremity more and more demineralises because of the absence of a sufficient mechanical stimulus [9, 16]. Therefore the correct region of interest to quantify the immobilisation osteoporosis in SCI patients is the lower limb e.g. the proximal femur.

At the lumbar spine there is no pathological result to expect. Some authors also do BMD measurements at the tibia [17]. We prefer the femur, because this region is also used in the diagnostic of idiopathic osteoporosis, large control groups exist and the ability to measure this region is widespread.

Table 1 Results of DEXA measurements at the proximal femur (mean $\pm$ SD)

Region of Interest prox. femur	Years after spinal cord injury				BMD- change <i>p</i> -value
	0-1		>5		
	BMD (g/cm ²)	Z-Score	BMD (g/cm ²)	Z-Score	
Femoral neck	0.842 ± 0.151	-0.238 ± 1.186	0.620 ± 0.167	-2.688 ± 1.882	<i>p</i> < 0.0001
Trochanteric region	0.657 ± 0.145	-0.883 ± 0.984	0.528 ± 0.197	-2.135 ± 1.846	<i>p</i> = 0.0028
Intertrochanteric region	1.007 ± 0.197	-1.179 ± 1.151	0.742 ± 0.307	-3.337 ± 1.604	<i>p</i> < 0.0001
Wards triangle	0.711 ± 0.194	0.234 ± 1.334	0.511 ± 0.223	-2.036 ± 2.403	<i>p</i> = 0.0002
Prox. femur (total)	0.889 ± 0.169	-0.658 ± 1.316	0.633 ± 0.188	-2.773 ± 1.786	<i>p</i> < 0.0001

Table 2 Results of DEXA measurements at the lumbar spine (mean $\pm$ SD)

Region of interest lumbar spine	Years after spinal cord injury				BMD-change <i>p</i> -value
	0–1		> 5		
	BMD (g/cm ²)	Z-score	BMD (g/cm ²)	Z-score	
L1	0.932 ± 0.152	−0.175 ± 1.216	1.042 ± 0.192	0.279 ± 1.775	<i>p</i> = 0.0084
L2	1.000 ± 0.172	−0.300 ± 1.231	1.096 ± 0.199	−0.062 ± 1.764	<i>p</i> = 0.0246
L3	0.999 ± 0.187	−0.273 ± 1.538	1.114 ± 0.224	0.134 ± 2.176	<i>p</i> = 0.0172
L4	0.977 ± 0.181	−0.706 ± 1.588	1.118 ± 0.215	−0.279 ± 2.197	<i>p</i> = 0.0039
LWS total (L1–L4)	0.978 ± 0.163	−0.315 ± 1.577	1.094 ± 0.200	0.008 ± 1.819	<i>p</i> = 0.0083

Table 3 Differences of the BMD between paraplegic and tetraplegic patients (mean $\pm$ SD); *p*-values. no significant difference between both groups

Region of interest	Years after spinal cord injury			
	0–1		> 5	
	Paraplegic patients Mean $\pm$ SD	Tetraplegic patients Mean $\pm$ SD (<i>p</i> -value)	Paraplegic patients Mean $\pm$ SD	Tetraplegic patients Mean $\pm$ SD (<i>p</i> -value)
BMD prox. Femur (g/cm ²)	0.855 $\pm$ 0.160	0.924 $\pm$ 0.176 (0.4082)	0.671 $\pm$ 0.172	0.593 $\pm$ 0.203 (0.2279)
BMD Lumbar Spine (g/cm ²)	0.974 $\pm$ 0.214	0.981 $\pm$ 0.113 (0.9232)	1.097 $\pm$ 0.189	1.089 $\pm$ 0.247 (0.9548)

Fig. 3 Boxplot of BAP in short-term (0–1 year) and long-term SCI patients (>5 years); no significant change between both groups; both groups slightly below normal range **Fig. 4** Boxplot of PYD in short-term (0–1 year) and long-term SCI patients (>5 years); significant decrease between both groups; both groups are clearly above normal range

There were no differences between tetraplegic and paraplegic patients in short-term and long-term SCI patients in the BMD. This also confirms the results of former studies [1, 5, 8, 10] and confirms the thesis that

the most important factor for stimulating bone-turn-over is the mechanical stimulus on the bone whereas the neurological height of the lesion has no significant effect on BMD-change.

Fig. 5 Boxplot of DPD in short-term (0–1 year) and long-term SCI patients (>5 years); significant decrease between both groups; both groups are clearly above normal range

Fig. 6 Boxplot of NTx in short-term (0–1 year) and long-term SCI patients (>5 years); significant decrease between both groups; both groups are above normal range

Until now only few studies have simultaneously examined BMD and the response of biochemical markers of bone turnover in patients with SCI [5, 11, 17].

The significant enhancement of all cross-links (PYD, DPD and NTx) shows the high activity of bone resorption not only in short-term but also in long-term SCI patients even after more than five years. Though in short-term SCI patients the bone resorption process is more active than in long-term SCI patients, the bone formation is not stimulated in both groups. The bone formation marker BAP is even slightly below normal range.

Similar results were described not only in patients with SCI [11, 17], but also in patients that were forced to bed rest for months because of apoplexy or senility [2, 6]. In these patients, the cross-links were clearly elevated and the BAP was in normal range, too. In SCI patients the few existing studies also describe elevated cross-links and normal BAP in short-term SCI patients [11, 17]. The problem of the immobilisation osteoporosis of SCI patients is the disproportion between high bone resorption and the absence of reactive bone formation. We found elevated cross-links not only in short-term but also in long-term SCI patients, which shows that the bone resorption is still active in these patients even after more than five years.

Since treatment interventions based on physical activity like placing the patients in an upright standing position aiming at preventing or even reversing the

process of bone loss after SCI have no sufficient positive effects [9, 12], pharmacological therapy seems to be necessary. Considering the results of this study, not only for short-term SCI patients but also for long-term SCI patients osteoclast inhibiting drugs like e.g. bisphosphonates seems to be most effective. Few studies with bisphosphonates like e.g. Tiludronat [3] and Alendronat [18] are promising.

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