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Changes in biochemical markers of bone metabolism and BMD during the first year after a hip fracture

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ABSTRACT – We measured the levels of biochemical markers of bone formation and bone resorption in hip fracture patients preoperatively and after 6 and 12 months. Bone densitometry was done with quantitative computer tomography (QCT), dual-energy X-ray absorptiometry (DXA) and heel ultrasound.

After 6 months, the biochemical markers of bone formation and bone resorption had increased. The levels remained high after 1 year and no change occurred between 6 and 12 months. We found no correlations between biochemical bone markers and bone density/stiffness on admission and change in bone mineral density (BMD) during the first postoperative year, despite the changes in bone markers and bone density.

In our opinion, biochemical bone markers can not be used to predict bone loss in the individual patient after a hip fracture.

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Bone changes occur in the hip after a fracture, as shown by histomorphometry, absorptiometry and QCT, (Nilsson and Westlin 1977, Obrant 1984, Terjesen et al. 1985).

Bone metabolism and bone turnover may be estimated indirectly by determining biochemical markers of bone formation and bone resorption. The consequences of a fracture on bone turnover and on bone metabolic markers are not fully known, but bone turnover seems to change after a hip fracture, the levels of bone formation markers having risen, at least during the first postoperative months (Nilsson and Westlin 1972, Åkesson et al. 1995). We studied the changes in biochemical markers for bone formation and bone resorption in patients with hip fractures during the first postoperative year. We also wished to determine whether biochemical bone markers could predict bone loss after surgery.

Patients and methods

Between January 1994 and December 1996, we included 32 patients, 11 with femoral neck fractures and 21 with pertrochanteric fractures. Patients who had been treated for osteoporosis during the previous year or had a metabolic disease that could affect bone density were excluded. Smokers and those with a previous fracture in the other hip were also excluded. Only patients living independently were included. Their mean age was 81 (69–89) years. The femoral neck fractures were operated on with two parallel screws and the pertrochanteric fractures with a sliding nail-plate, within 24 hours of admission. The study was approved by the local ethics committee. 4 patients died during the first 6 months and 1 after 9 months; 2 declined to participate for more than 6 months and 1 was excluded because of poor health. Thus 28 patients were followed for 6 months and 24 for 12 months.

The following biochemical bone markers were measured in serum: osteocalcin (NovoCalcin), C-terminal propeptide of type I collagen (PICP, Prolagen-C), bone-specific alkaline phosphatase (S-bALP, Alkphase-B) and in urine: deoxypyridinoline crosslinks (U-Dpd, Pyrilinks-D). All the measurements were done with ELISA kit methods from Metra Biosystems Inc., USA (Novatek Healthcare AB, Södertälje, Sweden). Serum C-terminal telopeptide of collagen type I (I-CTP) was measured with a 125-I RIA kit from Orion Diagnostica

Table 1. Biochemical bone markers (means (SD)) in the hip fracture group on admission and after 6 and 12 months, coefficients of variations (CV), reference values given by the manufacturer and means (SD) in the staff (aged 30–67)

	CV n 21	Reference values	Staff n 21	Admission n 32	6 months n 28	% change	P-value	12 months n 24
S-Osteocalcin (ng/mL)	3.6	3.7–10.0	9.5 (4.9)	9.1 (3)	12.2 (3)	+34	0.001	11.5
S-bALP (U/L)	4.7	11.6–30.6	15.7 (1.8)	21.5 (7)	22.9 (8)	+7	0.003	23.4
S-PICP (ng/mL)	5.1	69–147	113 (57)	73 (26)	109 (45)	+49	0.0001	115
S-ICTP (ug/L)	5.3	1.8-5.0	3.0 (1.8)	5.4 (3.5)	6.6 (2.5)	+22	0.003	6.9
U-Dpd (nM/mM creatinine)	3.2	3.0–7.4	7.9 (3.6)	8.0 (3.1)	10.5 (4.2)	+31	0.004	8.9

(Espoo, Finland).

Samples were run in duplicate. Controls included in the kits were run together with an independent control sample from a healthy donor to check reproducibility. Samples were taken in the morning (6–10 a.m.) and for U-Dpd, the first voided urine samples were used. Aliquots dispensed in polypropylene tubes were preserved at –70 °C for up to 12 months. Reference intervals given by the manufacturer for premenopausal women and means for 21 healthy subjects from the laboratory staff (aged 30–67 years) are shown in Table 1. The cross-reactivity of the anti-bALP monoclonal antibody for the liver isoenzyme was 3%–8%, according to the manufacturer.

BMD of the contralateral hip was determined with DXA using DPX-L (Lunar Corp. Madison, WI, USA). The precision error of the method as used by us was 2% for the hip measurements, i.e., as in earlier reports (Hansen et al. 1990, Lees and Stevenson 1992). DXA scans were performed 2–5 days after surgery.

QCT (General Electric Pace Plus, Milwaukee, Wisconsin) was used for bone density measurements of the proximal tibia, distal femur and mid-femur. The femurs were scanned 20 and 5 cm above the distal limit of the lateral femoral condyle and the tibia 2 cm below this reference point. Three circular regions of interest were chosen in the cortical bone in the mid-femur. The mean value was estimated as the bone mineral density in this location. The bone density was also measured by tracing around the distal femur and proximal tibia. The volumes of the thigh muscle were also measured 20 cm proximal to the distal limit of the lateral condyle. There is a difference in X-ray attenuation between fat, bone and muscle. By using thresholds for each tissue, the computer then calculates the volumes. The error in precision has been estimated at 2% for bone mineral density in the proximal femur, 4% and 5% in the distal femur and proximal tibia and 3% for muscle volume in the mid-femur. These estimates were made in our department with the same equipment (Neander et al. 1997a), and are similar to those reported elsewhere (Steiger et al. 1990, Karantanas et al. 1991).

Ultrasound velocity; speed of sound (SOS), broad-band ultrasound attenuation (BUA) and stiffness (BUA-50) × 0.67 + (SOS + 1380) × 0.28) were measured with heel ultrasound using an Akchilles densitometer (Lunar Corp. Madison, WI, USA). The precision error of this method is 2–4% (Truscott et al. 1992), which agrees with our measurements.

Statistics

We used the Student's t-test for unpaired and paired observations and correlation analysis. Biochemical markers of bone metabolism and BMD were regarded as normally distributed. A p-value less than 0.05 was considered significant. The Bonferroni method was used to correlate multiple comparisons. The evaluations were performed with the JMP PC program.

Results

A significant increase was found in all bone markers between admission and the 6-month follow-up (Table 1). There were no significant changes in bone markers between 6 and 12 months, markers of bone formation and markers of bone resorption remaining higher than the levels on admission.

The biochemical bone markers on admission and after 6 months had few and weak correlations with

Table 2. Bone mineral density changes during the first year after surgery (mean % difference)

	6 months / 0 months n 28	12 months / 0 months n 24
QCT, operated leg		
Proximal femur	–2	–4 [a]
Distal femur	–18 [a]	–23 [a]
Proximal tibia	–26 [a]	–25
Unoperated leg		
Proximal femur	0	–1
Distal femur	–4	–7
Proximal tibia	–7 [a]	–3
Heel ultrasound, operated leg		
BUA	–3 [a]	–0.5
Stiffness	+3 [a]	+1
DXA, unoperated hip		
Trochanter	–3 [a]	–4 [a]

[a] $p < 0.05$

the 1-year change in bone density/stiffness and after a Bonferroni correction for multiple comparisons there were no significant correlations left. We found a significant loss of BMD 6 and 12 months postoperatively, measured with DXA and QCT, most marked in the trabecular bone in the proximal tibia and distal femur. Heel ultrasound, however, showed a significant reduction in BUA, but an increase in stiffness during the first 6 months (Table 2). The increase in thigh muscle volume in the unoperated leg was also significant during the first 6 months.

Discussion

It has been suggested that hip fracture patients have normal or low bone formation and increased bone resorption before a fracture occurs, compared to age-matched healthy women, i.e., an imbalance of bone turnover (Åkesson et al. 1993, Garnero et al. 1996). This agrees with our results showing normal levels of bone formation markers and high levels of bone resorption markers in hip fracture patients on admission. This metabolic disorder could be a part of the development of osteoporosis in this group of patients.

We obtained our samples in the morning within 18 hours of the hip fracture and therefore it is difficult to distinguish prefracture abnormalities in bone turnover from confounding effects of the trauma, such as changes in body fluids and stress-hormone-induced effects on bone metabolism. However, it has been shown that the osteocalcin level is independent of the time elapsed since trauma, within 18 hours, whereafter the level decreased until the third postoperative day (Åkesson et al. 1993). Prospective studies are still needed where bone markers are measured immediately before the fracture and a time-perspective must be used for earlier fractures when the levels of bone markers are estimated.

An increase in osteocalcin has been found during the first 4–7 months after a hip fracture (Åkesson et al. 1995). We saw changes in all biochemical bone markers during the first year after a hip fracture: both bone formation markers and bone resorption markers were significantly increased after 6 months and remained high after 12 months, indicating increased bone turnover (Table 1).

The densitometry measurements showed a loss of BMD in the operated leg during the first year postoperatively. The main loss was seen in the trabecular bone in the distal femur and proximal tibia measured with QCT. A significant loss of BMD in the unoperated hip was also measured with DXA (Table 2), similar to what others have found (Karlsson et al. 1996, Neander et al. 1997b), indicating general posttraumatic osteopenia.

The high bone turnover, as assessed by biochemical markers, may be associated with the posttraumatic osteopenia and/or fracture healing. The increase in bone metabolic activity could also be partly due to an increase in physical activity during rehabilitation with an increase in thigh muscle volume in the unoperated leg.

Despite our findings of signs of changed bone metabolism in the biochemical analysis and the densitometry measurements, we found no correlations between bone markers and the ultrasound, DEXA and QCT measurements during the first postoperative year. Similar to what others have found, BMD was not correlated to bone markers (Cheng et al. 1996). Osteoporosis is probably a heterogeneous disorder, which would explain the great inter-individual variation in biochemical bone markers, besides the intra-individual variability (Beck Jensen et al. 1997). They are therefore unsuitable for prediction of bone loss in the individual patient.

Bone markers can expand our knowledge of the pathophysiology of bone metabolism and fracture healing, but in our hands, they can not be used to identify patients at risk of bone loss after hip fracture.

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