Biochemical bone markers and bone density in hip fracture patients

Weak correlation in 106 women

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ABSTRACT – Biochemical markers of bone formation and bone resorption were measured preoperatively, within 18 hours after a hip fracture (n 106) and bone mineral density (BMD) was measured with quantitative computer tomography (QCT), dual-energy x-ray absorptiometry (DXA) and heel ultrasound in 63 hip fracture patients.

Patients with pertrochanteric fractures had more osteoporosis in all measurements than patients with femoral neck fractures. We found no differences in biochemical markers of bone formation or bone resorption in patients with femoral neck fractures and in those with pertrochanteric fractures. Correlations between biochemical bone markers and bone density, bone mass and stiffness on admission were weak.

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Bone metabolism may be estimated indirectly by determination of bone formation and resorption markers. It has been suggested that hip fracture patients have a normal or low bone formation activity and an increased bone resorption before a fracture compared to age matched healthy women (Åkesson et al. 1993, Garnero et al. 1996). It is well known that patients with hip fractures have lower BMD than age-matched persons without a fracture (Karlsson et al. 1993) and there is a relationship between the bone density and fracture of the hip (Hui et al. 1988, Cummings et al. 1990). Patients with hip fractures are still regarded as a single population, although there is a considerable difference in the physical condition and the radiographic bone findings between those with femoral neck fractures and those with pertrochanteric fractures (Lawton et al. 1983, Sernbo et al. 1989).

We investigated whether there were any differences in bone metabolism by measuring the biochemical bone markers in patients with femoral neck fractures and in those with pertrochanteric fractures. We also assessed any correlations between BMD, bone mass, stiffness and bone markers on admission.

Patients and methods

We included 106 women, 48 patients with femoral neck and 58 with pertrochanteric fractures, mean age 79 (7) and 82 (5) years, respectively. The patients with femoral neck fractures were operated on with 2 parallel screws and those with pertrochanteric fractures with a sliding nail-plate within 24 hours after admission to hospital. Patients who had been treated for osteoporosis during the last year or had any metabolic disease that could influence bone density were excluded. Smokers and those who had previously sustained a fracture in the other hip were also excluded. Only patients living independently in their own homes were included.

Blood and urine samples were obtained in the morning, within 18 hours after fracture (n 106), and bone densitometry was performed 2–5 days after surgery, if MH was available (n 63).

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, which were all 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 (Espoo, Finland).

Samples were run in duplicate. Controls included in kits were run together with an independent control sample from a healthy donor to check reproducibility. Sampling was performed in the morning (6–10 am) and, for U-Dpd, the first voided urine samples were used. After dispensing of aliquots in polypropylene tubes, they were preserved at –70 °C for up to 12 months. Reference intervals for 21 healthy subjects on the laboratory staff (ranges within parentheses for the subgroup of postmenopausal women, and means (SD) for all persons, aged 30–67 years, respectively) were: serum osteocalcin (6.3–23.3 ng/mL, n 11) 9.5 (2.4), n 20; serum PICP (90–155 ng/mL, n 11), 113 (28), n 21; serum bALP (13.7–34.3 U/L, n 11), 15.7 (0.9), n 21; serum ICTP (2.8–5.6, g/L n 11), 3.0 (0.9), n 21; urinary Dpd (3.4–8.1 nM/mM creatinine, n 11), 7.9 (1.8), n 20. The analytical imprecision (% CV) was found to be 3.6, 4.7, 5.1, 5.3, and 3.2, respectively. The cross-reactivity of the anti-bALP monoclonal antibody for the liver isoenzyme was 3–8% according to the manufacturer.

We also measured serum albumin, weight and length. Clinical assessment before the fracture was determined by using the Harris hip scoring system.

BMD of the contralateral hip, i.e., femoral neck and lumbar spine, were determined by DXA using DPX-L (Lunar Corp., Madison, WI, USA). The standard deviation of BMD in hip fracture patients, compared to the mean BMD in young adults and age-matched normal subjects, was expressed as the T and Z scores. The precision error of the method was 1.3% for the lumbar spine and 2% for the hip measurements in our hands, which is similar to the values reported earlier (Hansen et al. 1990, Lees and Stevenson 1992).

DXA scans were performed 2–5 days after surgery. QCT (General Electric Pace Plus, Milwaukee, WI) was used for bone density measurements of LI-LIII in the lumbar spine, proximal tibia, distal femur and the middle 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. 3 circular regions of interest were chosen in the cortical bone in the middle femur and the mean value was estimated as the bone mineral density at this location. The bone density in this region was measured by making a tracing around the distal femur and the proximal tibia. We measured the bone density in the lumbar spine by choosing three circular regions of interest in the trabecular bone in each vertebra and the mean value of the three regions of interest was estimated to be the bone mineral density at that location.

The volumes of the thigh muscle were 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 and, by using thresholds for each tissue, the computer then calculates the volumes. We calculated the bone mass as the bone mineral density multiplied by the bone volume at that location. The precision error has earlier been estimated at 2% for bone mineral density in the middle femur, 4% and 5% of the distal femur and the proximal tibia, respectively, and 3% for muscle volume of the the middle femur in our department with the same equipment (Neander et al. 1997). These values are similar to those that others have found (Steiger et al. 1990, Karantanas et al. 1991).

We measured the ultrasound velocity speed of sound (SOS), broad band ultrasound attenuation (BUA) and the stiffness (BUA-50) × 0.67 + (SOS + 1380) × 0.28) with heel ultrasound, using an Akilles densitometer (Lunar Corp. Madsion, WI, USA). The precision error of this method has been found to be 2–4% (Truscott et al. 1992), which is in agreement with what we have found.

The Student's t-test was used for unpaired and paired observations, as well as regression analysis. The statistical software JMP was used in the statistical analysis. A p-value less than 0.05 was considered significant.

Results

Patients with femoral neck fractures were less osteoporotic in the hip (DXA), and in the other mea-

Table 1. Differences in biochemical bone markers and bone densitometry measurements between patients with femoral neck fractures and pertrochanteric fractures on admission (mean (SD))

	Pertrochanteric group n 35	Femoral neck group n 28	P-value
DEXA measurements (g/cm²) (n 63), (unoperated hip)			
BMD lumbar spine	0.9 (0.19)	1.0 (0.13)	0.02
BMD wards	0.5 (0.11)	0.6 (0.11)	0.0007
BMD neck	0.6 (0.12)	0.7 (0.09)	0.004
BMD trochanter	0.5 (0.12)	0.6 (0.12)	0.002
T-score femoral neck (SD)	–3.0 (0.98)	–2.3 (0.79)	0.005
Z-score femoral neck (SD)	–1.1 (0.87)	–0.4 (0.67)	0.003
T-score ward (SD)	–3.4 (0.86)	–2.6 (0.88)	0.0007
Z-score ward (SD)	–1.1 (0.14)	–0.3 (0.15)	0.0005
T-score trochanter (SD)	–2.3 (0.75)	–1.5 (1.1)	0.003
Z-score trochanter (SD)	–1.2 (0.54)	–0.4 (1.0)	0.0005
QCT measurements (g/cm³) (n 63), (operated leg)			
Distal femur	132 (36)	158 (45)	0.01
Proximal tibia	59 (22)	74 (23)	0.009
L II	50 (28)	66 (25)	0.02
L III	52 (34)	62 (27)	0.05
Thigh muscle volume	43 (12)	47 (12)	0.2
Heel ultrasound (n 63), (operated leg)			
SOS (speed of sound)	1463 (42)	1484 (44)	0.02
BUA (broad band ultrasound attenuation)	91 (8.3)	98 (9.9)	0.007
Stiffness (BUA–50) x 0.67+ (SOS+1380) x (0.28)	51 (10)	62 (12)	0.0006
Biochemical bone markers (n 63), (106)			
S-Osteocalcin (ng/mL)	8.8 (2.2)	9.4 (3.7)	0.5
S-Osteocalcin (ng/mL)	**9.9 (4.4)**	**11 (7.1)**	**0.5**
S-bALP (U/L)	21 (7.4)	19 (6.0)	0.2
S-bALP (U/L)	**21 (7.4)**	**22 (8.5)**	**0.8**
S-PIPC (ng/mL)	72 (27)	75 (41)	0.8
S-PIPC (ng/mL)	**78 (41)**	**70 (37)**	**0.3**
S-ICTP (Ug/mL)	5.3 (3.3)	6.0 (4.9)	0.5
S-ICTP (Ug/mL)	**6.0 (4.4)**	**6.5 (5.5)**	**0.6**
U-Dpd (nM/mM creatinine)	8.0 (3.0)	7.5 (2.7)	0.6
U-Dpd (nM/mM creatinine)	**8.0 (3.0)**	**8.5 (4.0)**	**0.5**
Descriptive clinical and biological data (n 63)			
Harris hip score	89 (10)	92 (8.8)	0.3
Weight (kg)	60 (12)	62 (9.8)	0.5
Length (cm)	160 (6)	163 (6)	0.1
BMI (%)	23 (4)	23 (4)	0.8
Serum albumin (g/L)	37 (0.8)	39 (0.9)	0.2
Age (years)	82 (6)	79 (7)	0.1

Bold lettering indicates n 106

sured sites—i.e., in the middle of the femur, distal femur, proximal tibia (QCT), calcaneus (heel ultrasound) and the lumbar spine (DXA), compared to patients with pertrochanteric fractures (Table 1).

We found no significant differences in biochemical markers of bone formation or bone resorption on admission between patients with femoral neck and pertrochanteric fractures (Table 1). Serum osteocalcin and serum bALP were normal and serum PICP was low in both groups, compared to our reference group and both groups had high levels of serum ICTP. We found no significant differences in serum albumin, age, weight, length or hip score between the groups on admission.

After adjustment for age, we found a weak correlation between high levels of Dpd, osteocalcin and ALP with low bone density and stiffness on admission (Table 2). There was no difference in the balance between formation and resorption (PICP/ICTP) between the groups.

Discussion

Most hip fracture patients had low BMD (Table 1).

Low radiographic bone density in hip fracture patients was first described by Vose and Lockwood (1965) and confirmed by others (Chevalley et al. 1991, Duboeuf et al. 1991). Later, Sernbo et al. (1989) reported a radiographic difference between those with pertrochanteric fractures and those with femoral neck fractures. Chevalley et al. (1991) found no differences in femoral neck BMD between pa-

Table 2. Correlation coefficients (r) for biochemical bone markers and various BMD and bone mass on admission, after adjustment for age (n 63); only significant values are given (p < 0.05)

	S-osteocalcin	S-bALP	S-ICTP	U-Dpd	S-PIPC
QCT (operated leg)					
BMD prox femur	–	–	–	–0.4	–
Bone mass	–	–	–	–	–
BMD distal femur	–0.4	–0.4	–	–0.4	–
Bone mass	–0.3	–	–	–0.5	–
BMD prox. tibia	–0.3	–	–	–	–
Bone mass	–0.3	–	–	–0.3	–
LI	–	–	–	–0.3	–
LII	–	–	–	–0.4	–
LIII	–	–	–	–	–
DXA (unoperated leg)					
Neck	–0.3	–	–	–0.4	–
Wards	–0.3	–	–	–0.5	–
Trochanter	–0.4	–	–	–0.4	–
Lumba spine	–	–	–	–	–
Heel ultrasound (operated leg)					
BUA	–0.3	–	–	–0.4	–
SOS	–	–	–	–0.3	–
Stiffness	–0.4	–0.3	–	–	–

tients with pertrochanteric fractures, compared to those with femoral neck fractures while Karlsson et al. (1993) found a lower BMD in the spine and trochanter in patients with pertrochanteric fractures. This is in agreement with our results, but in addition to this, we found lower BMD values in all locations evaluated with QCT, DXA and ultrasound in the pertrochanteric group. These findings indicate a biological difference and possibly a different bone metabolism between patients with pertrochanteric and femoral neck fractures.

We observed a tendency to low formation (s-PICP) and an increased bone resorption (S-ICTP) in both groups, similar to that has been found in hip fracture patients shortly after admission (Åkesson et al. 1993). It has been suggested that elderly women at greater risk for hip fracture, i.e., with low BMD, show increased bone resorption (Garnero et al. 1996).

When bone markers in fracture patients are evaluated, the time of fracture must be considered. It is almost impossible to obtain biochemical bone markers immediately before a fracture. However, no data are available whether samples obtained on admission to hospital are representative of the state prior to fractures. But it has been shown that the osteocalcin level is independent of the time elapsed after a trauma, within 18 hours. Thereafter the level decreased until the third postoperative day (Åkesson et al. 1993).

Bone markers and bone-density parameters have been shown to be correlated, if patients with fractures and controls without fractures are included (Garnero et al. 1996). When, as in this study, to reduce variation, only women with fractures, living independently on their own and with no previous fracture of the other hip were included, correlations between biochemical markers of bone metabolism and bone density on admission were weak.

Despite a considerable difference in BMD between patients with pertrochanteric fractures and those with femoral neck fractures in our study, there was no difference in the biochemical markers of bone formation nor in the markers of bone resorption. A different bone metabolism with higher bone turnover, measured with biochemical bone markers, did not explain the lower BMD values in the pertrochanteric group.

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