Low IGF-I levels in hip fracture patients

A comparison of 20 coxarthrotic and 23 hip fracture patients

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We measured total body bone density and body composition with dual energy x-ray absorptiometry in 43 elderly patients, 23 with hip fracture and 20 with coxarthrosis, after surgery and after 6 months. Insulin-like growth factor-1 (IGF-I), a polypeptide known to affect bone metabolism, and two of its binding proteins (IGFBP-1, IGFBP-3) were measured preoperatively and after 6 months. Normal serum IGF-I levels are dependent on adequate nutrition and normal secretion of growth hormone (GH). We found consistently lower levels of IGF-I and IGFBP-3 and a tendency to higher levels of IGFBP-1 in the patients with hip fractures, who also had a lower total body mass, lower fat mass and bone mineral density than the coxarthrosis group, indicating a more catabolic state in the patients with hip fracture, even 6 months after the trauma.

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Hip fracture in the elderly following low energy trauma is often a consequence not only of a fall but also of osteoporosis and a general catabolic state. Growth hormone (GH) has anabolic effects on both bone (Brixen et al. 1993) and skeletal muscle (Fryburg and Barret 1993). These effects may be mediated by GH directly or by insulin-like growth factor 1 (IGF-I) and modified by the 6 binding proteins (IGFBP 1-6). Circulating IGF-I levels generally correlate well with GH secretion in healthy well-nourished patients having normal GH responsiveness. GH stimulates IGF-I production in the liver and also in extrahepatic sites such as muscle, bone and adipose tissue. IGFBP-3 increases with GH secretion while the IGFBP-1 concentration is mainly insulin-regulated and its production is inhibited by insulin. We investigated whether IGF-I, IGFBP-1 and IGFBP-3 differed in patients with hip fractures, compared to patients undergoing surgery for coxarthrosis. We also investigated whether circulating IGF-I and IGFBP levels correlated with total body composition and bone mineral density (BMD).

Patients and methods

The study started in November 1994 and lasted until October 1995. 10 men and 13 women over 60 years of age with a hip fracture were recruited consecutively. As a control group, 10 men and 10 women with primary coxarthrosis, scheduled for a total hip replacement were included consecutively in two groups, one between 60 and 75 years and one over 75 years of age. Patients were not included if the project leader, MH, was not available, if they were smokers or had taken any drugs known to affect bone metabolism during the last 6 months. Patients who had previously sustained a fracture in the contralateral hip were also excluded. Only those living independently in their own homes were included. Mean age was 80 (64–93) years in the hip fracture group and 77 (66–89) years in the coxarthrosis group. The hip fracture group consisted of 13 patients with femoral neck fractures and 10 with pertrochanteric fractures. The patients with femoral neck fractures were operated on with 2 parallel screws and those with pertrochanteric fractures with a sliding nail-plate. Those with coxarthrosis underwent a cemented total hip replacement.

2 presumptive patients from the hip fracture group could not participate in the study because of postoperative complications and 1 from the coxarthrosis group declined to participate.

2 hip fracture patients, who were included, died, 1 patient with coxarthrosis could not be followed up due to bad health and 1 had moved to another region. The laboratory tests in 4 patients at the 6-month follow-up were not analyzed because of mistakes in the sampling. Therefore, DXA measurements were made in 39 of 43 patients at 6 months but blood samples were analyzed in only 35.

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BMD of the total body (g/cm^2) and body composition were determined with dual energy x-ray absorptiometry (DXA) using a Lunar DPX-L, Scanner (Lunar Corp. Madison, WI, USA). The precision of the method has been shown to be 0.5% for total body BMD (Lunar Corp) and the coefficient of variation (CV) for the total body BMD in our measurements was 1%. The software used for DXA scan analysis excluded high density pixels (metal implants). DXA scans were performed at 2–5 days and 6 months after surgery and thus the implants were present in all patients at both measurements.

Table 1. Mean (SD) values on admission of various parameters and comparison between the groups

	Hip fracture group	Coxarthrosis group	P-value
Number	23	20	
Age	80	77	
Female/male	10/13	10/10	
Total body fat, kg	19 (7.5)	25 (6.4)	0.01
Total lean body mass, kg	45 (7.6)	45 (6.8)	0.7
Total body mass, kg	63 (10.9)	70 (8.2)	0.04
BMD, g/cm^2	0.99 (0.1)	1.10 (0.1)	0.006
S-IGF-1, ng/mL	71 (28.7)	92 (31)	0.02
S-IGFBP-1, ng/mL	36 (31.8)	26 (15)	0.2
S-IGFBP-3, mg/mL	3.0 (0.8)	3.4 (1.0)	0.08
Body mass index, BMI,%	21.8 (0.4)	24.4 (0.3)	0.03
S-albumin, g/L	37 (5.8)	40 (4.9)	0.1

Fasting blood samples were collected by venipuncture in the morning within 18 hours of admission in the hip fracture group and just before surgery in the coxarthrosis group. Blood samples were repeated 6 months later. After centrifugation, sera were frozen at –70 °C, pending use. Serum albumin was analyzed with the absorption photometry technique. Serum IGF-I and IGFBP-1 were measured with a specific radioimmuno-assay (Kabi Pharmacia, Sweden), using polyclonal rabbit antiserum. The immunocomplexes were precipitated with a second antibody in a polyethyleneglycol environment before measurement in a gamma counter. IGFBPs were separated from IGF-I with acidified ethanol extraction prior to assay. To reduce further the influence of the IGFBP activity, a truncated IGF-I analogue des (1-3) rhIGF-I ws utilized as tracer. Normal values of IGF-I based on 29 healthy subjects aged 60–71 years (Kabi Pharmacia) show a mean concentration of 119 ng/mL (SD 33). At a concentration of 201 ng IGF-I/mL, the intra-assay and inter-assay coefficients of variations were 3.1% and 10%, respectively. IGF bound to IGFBPs in serum has no significant diurnal rhythm and a half-life of about 12–16 hours in fasting healthy subjects (Zapf 1997).

Normal mean values for serum IGFBP-1 based on 148 non-fasting subjects (mean age 44 years) was 12 (1–35) ng/mL and for 37 fasting subjects (mean age 38 years) 33 (4–167) ng/mL. The intra-assay and inter-assay variations were 3.2% and 12%, respectively, at a concentration of 12.4 ng/mL. A diurnal rhythm of IGFBP-1, with high concentrations between 03.00 and 09.00 and relatively constant low concentrations between 13.00 and 24.00, has been reported in adults (Degerblad et al. 1989). Hypoinsulinemia increases and hyperinsulinemia decreases the IGFBP-1 concentrations (Brismar et al. 1988). The half-life of IGFBP-1 is about 90–120 minutes (Brismar et al. 1994).

The serum IGFBP-3 concentration was measured with an enzyme-linked immunosorbent assay technique (commercial kit from Diagnostic System Laboratories Inc., Webster, Texas, USA). Inter-assay CVs were 5.5% at 6.0 ng/mL and 5.2% at 21 ng/mL. Reference values based on 28 healthy subjects aged 60–71 years (Kabi-Pharmacia) show a mean concentration of 2.16 (1.1–3.3) mg/mL.

The study was approved by the local ethics committee.

Statistics

Differences between groups were tested with the Student's t-test. Correlations were computed with Pearson's method. A multiple linear regression analysis with stepwise backward variable elimination was performed to estimate the effects of 4 significant variables from the univariate analysis on the variation in BMD at 6 months postoperatively to avoid influence of the trauma. All tests were two-tailed and p-values below 0.05 were considered to be significant.

Results

On admission

The mean serum IGF-1 ($p = 0.02$) and IGFBP-3 ($p = 0.08$) levels were lower and the IGFBP-1 ($p = 0.2$, n.s.) level tended to be slightly higher in the hip fracture group than in the coxarthrosis group (Table 1). The hip fracture patients had lower total body BMD, body mass and fat mass compared to the coxarthrosis group (Table 1). There was a positive correlation between IGF-1 and IGFBP-3 ($r = 0.5$) and a negative correlation between IGF-1 and IGFBP-1 ($r = -0.5$).

After 6 months

The hip fracture patients' total body BMD, lean body

Table 2. Mean (SD) differences in total body scan values between admission and 6 months' follow-up

	Hip fracture group		Coxarthrosis group	
	Changes at 6 months	P-value	Changes at 6 months	P-value
Total body lean mass, kg	–2.1 (2.5)	0.0001	–1.2 (1.9)	0.01
Total body fat mass, kg	–1.0 (1.9)	0.04	–0.3 (1.8)	0.9
Total body mass, kg	–3.1 (3.1)	0.0003	–1.2 (2.7)	0.06
BMD, g/cm^2	–0.02 (0.04)	0.04	0.01 (0.07)	0.5

Table 3. Variables that influence BMD (g/cm^2), after 6 months, as determined by multiple regression analysis, incorporating weight, age, IGF-1 and IGFBP-3 (35 patients)

	Model 1			Model 2		
	Coeff	P-value	R-square	Coeff	P-value	R-square
Intercept	0.55			0.46		
Weight	0.006	0.0009	0.56	0.007	0.0002	0.56
IGF-1	0.001	0.06		0.001	0.02	
IGFBP-3	–0.006	0.7				
Age	–0.0007	0.8				

mass and fat mass decreased significantly during the first 6 months postoperatively, in contrast to patients with coxarthrosis who lost only significant amounts of lean body mass during this period (Table 2). Serum IGF-1 ($p = 0.001$) and IGFBP-3 ($p = 0.02$) values were lower in the hip fracture group. Body weight together with IGF-1 explained 56% of the variations in total body BMD (Table 3).

Discussion

In healthy young men, serum IGF-1 and IGFBP-3 were positively correlated with BMD (Johansson et al. 1994) and similar results have been found in healthy elderly men (Høidrup et al. 1996).

We found lower serum IGF-1 and IGFBP-3 levels in the hip fracture group who also had lower total body BMD. Our results are in accordance with the results of a previous study on patients with vertebral fractures and osteoporosis who also had lower levels of IGF-1 and IGFBP-3 than patients with spondylarthrosis and a group of healthy individuals (Wüster et al. 1993).

We compared hip fracture patients to patients with coxarthrosis. A reference group of healthy, age-matched individuals having comparable orthopedic trauma is difficult to find, and it must be kept in mind that patients with coxarthrosis probably have a higher BMD than normal age-matched subjects (Lloyd et al. 1996).

Nutrition influences not only IGFBP-1 production and circulating IGF-1 levels but also the receptor/binding protein for GH. Earlier studies have shown a low GH receptor/binding protein and GH resistance in undernourished children (Postel-Vinay et al. 1995) and it has been suggested that this effect is reversible with refeeding (Counts et al. 1992).

The hip fracture patients had lower BMI, lower total body mass, lower total body fat mass and BMD than the coxarthrosis group on admission. This, together with the tendency to lower serum albumin level on admission in the hip fracture group, could be a sign of prefracture catabolism. The hip fracture patients also lost tissue in all compartments postoperatively while the coxarthrosis group had a significant loss in lean body mass only.

Major surgery or other causes of extensive trauma induce a catabolic state associated with increases in growth hormone levels and a decrease in circulating IGF-1, suggesting a GH-resistant state (Ross et al. 1991). The decrease in circulating IGF-1 has been found within 34 h of the operation (Cwyfan Hughes et al. 1992). The influence of skeletal injury and trauma on growth factors and binding proteins is only partly known, therefore the values 6 months postoperatively were expected to reflect the habitual situation best and were chosen in the multiple regression analysis.

In conclusion, there were differences regarding body composition, IGF-1 and binding proteins between the groups, although we selected relatively "healthy" individuals in the hip fracture group; they

came from their own homes and had their first hip fracture. In a more representative group of frailer hip fracture patients, the differences might be even more pronounced. The positive relationship between BMD and circulating IGF-1 suggests that IGF-1 is of positive importance for bone mass. Our findings suggest that decreased levels of the GH-related growth factor IGF-1 due to catabolism and/or GH resistance could be involved in the pathogenesis of senile osteoporosis. There is a need for studies to assess the therapeutic potential of growth hormone/growth factors, together with adequate nutrition, in attenuating bone and muscle loss in elderly patients having hip fractures.

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