

3rd Black Forest Forum
for Musculoskeletal Interactions,
May 4-7, 2006

Trabecular bone modeling and subcapital femoral fracture

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Abstract

Fragility fractures, including neck of femur fractures, result from reductions in the amount, quality and architecture of bone. The aim of this study was to compare the cancellous bone structure, and static indices of bone turnover, in female patients who had sustained fragility fracture at the femoral neck, with age-matched females without fragility fracture. Bone samples were taken from the intertrochanteric region of the proximal femur of female patients undergoing hip arthroplasty surgery for a subcapital fragility fracture of the femoral neck (#NOF) or from age-matched female control individuals at routine autopsy. The histomorphometric data, which were normally distributed, indicated no difference between the mean values for any of the structural parameters in control and fracture samples. In particular, the BV/TV values were not different and did not change significantly with age in these cohorts of individuals aged >65 years. The static indices of bone turnover, eroded surface (ES/BS) and osteoid surface (OS/BS), were positively correlated with age in the >65-year-old control group ($p < 0.05$ and $p < 0.03$, respectively). The median values for these indices were not different between the fracture and control groups. However, both the median and the range of OS/BS values were increased for >65-year-old controls compared with a group of younger females aged <65 years, suggesting an increase in bone formation in older females in the proximal femur after 65 years of age. When the data were further interrogated, a reduction in the percentage osteoid surface to eroded surface quotient (OS/ES) was found for the fracture group compared with the age-matched control group. These data indicate that perturbations in bone formation and/or resorption surface are potentially important in producing bone in the proximal femur with increased propensity to fracture. These data also support the concept that trabecular bone modeling may be a factor influencing bone strength in addition to bone mass.

Keywords: Trabecular Bone Modeling, Trabecular Bone Remodeling, Subcapital Femoral Fracture, Bone Formation Surface, Bone Resorption Surface

Introduction

Remodeling is a process in which bone resorption precedes bone formation. This coupled sequence creates a scalloped cement line, which reflects previous osteoclast activity¹. Alternatively, modeling is the biological mechanism that adapts the skeleton to overloads, shaping and sizing it to provide mechanical competence, during usual physical activity². Frost² hypothesized that modeling can con-

tinue to occur in trabecular bone throughout life. Therefore, modeling may be more important in maturity than previously thought. Recent longitudinal studies indicated that the amount of periosteal expansion during aging varies among individuals³ and bone site⁴. This age-related bone modeling has been reported in cross-sectional studies⁵ and has been confirmed in longitudinal studies³ and by histological analyses⁶⁻⁸. A small amount of bone added periosteally or to trabeculae can offset the mechanical consequences of bone loss^{9,10}. The way in which bone remodeling and modeling relates to fracture at various sites requires further investigation, as does identification of the molecular factors that regulate bone turnover.

Changes in the remodeling of cancellous bone, resulting in both structural differences and a reduced amount of bone, have been identified in a range of human cancellous bone sites, including the vertebral body and iliac crest bone¹¹⁻¹³. We have measured structural parameters and static indices of bone turnover from the intertrochanteric region of the proximal

The authors have no conflict of interest.

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Accepted 25 August 2006

Histomorphometric Parameters	#NOF Females (age range 69-97 yrs) n=21	Control Females (age range 68-88 yrs) n=11	p value	Control Females (age range 18-60 yrs) n=15	p value
BV/TV (%)	7.1±4.3	6.5±3.7*	0.7	14.3±4.5*	0.00007*
BS/BV (mm ² /mm ³)	22.1±7.4	23.8±6.8*	0.5	15.7±6.6*	0.007*
BS/TV (mm ² /mm ³)	1.4±0.7	1.4±0.4*	0.9	1.9±0.5*	0.002*
Tb.Sp (microns)	1743±952	1478±491*	0.3	918±253*	0.004*
Tb.Th (microns)	99±30	91±28*	0.5	154±78*	0.01*
<i>Mean ± standard deviation.</i>					
O.Th (microns)	12.0 [6.7-20.5]**	7.5 [3.3-9.0]**	0.02**	5.6 [3.3-9.3]	0.9
ES/BS (%)	2.9 [2.1-4.9]	2.7 [2.1-3.9]	0.7	2.9 [1.2-3.2]	0.4
ES/BV (mm ² /mm ³)	0.6 [0.5-0.9]	0.6 [0.5-0.9]*	0.9	0.3 [0.2-0.4]*	0.02*
ES/TV (mm ² /mm ³)	0.04 [0.02-0.05]	0.03 [0.03-0.04]	0.6	0.05 [0.03-0.06]	0.2
OS/BS (%)	6.9 [4.8-11.7]	11.1 [8.2-14.0]*	0.2	2.9 [2.2-6.2]*	0.005*
OS/BV (mm ² /mm ³)	1.9 [0.7-2.8]	2.9 [1.6-3.9]*	0.2	0.4 [0.2-0.9]*	0.0002*
OS/TV (mm ² /mm ³)	0.1 [0.04-0.2]	0.1 [0.1-0.2]	0.2	0.05 [0.03-0.1]	0.06
OV/BV (%)	1.5 [1.0-2.3]	0.4 [0.6-3.5]*	0.7	0.2 [0.1-0.3]*	0.0005*
OV/TV (%)	0.07 [0.05-0.2]	0.07 [0.04-0.2]*	0.4	0.02 [0.02-0.04]*	0.008*
OS/ES (%)	2.1 [1.6-3.1]**	4.2 [2.9-5.3]**	0.02**	1.5 [0.8-4.8]	0.07
<i>Median [25th and 75th percentiles].</i>					

Table 1. Bone structural and turnover indices in female #NOFs, age-matched female controls and female controls aged <65 years intertrochanteric trabecular bone samples.

femur in hip fracture and age-matched elderly control individuals. We provide evidence suggestive of a relative reduction in bone formation surface compared with resorption surface in patients with fragility fracture of the femoral neck.

Materials and methods

Trabecular bone cores from the intertrochanteric region of the proximal femur were obtained from 21 postmenopausal female patients undergoing hip arthroplasty surgery for fragility subcapital fracture of the femoral neck (#NOF; 21 women, 69-97 years-old; mean age=81.5±8.2 [SD] years). An age-matched control group comprised 11 women, 68-88 years old (mean age=76.7±6.6 years), from whom bone samples were taken at autopsy. An additional control group comprising 15 younger women, 18-60 years old (mean age=33.1±15.0 years) was used for some comparisons. Control individuals were not known to have suffered from any disease affecting the skeleton. Patients with osteomalacia were excluded from both control study groups. Bone samples were processed for undecalcified histomorphometry, as described previously¹⁴. Histomorphometry was performed using an ocular-mounted 10x10 graticule at a magnification of x100. The histomorphometric parameters measured are listed in Table 1.

Statistical analysis. To test whether the data groups were either parametric or non-parametric the Shapiro-Wilk statistic was calculated using SAS software (SAS Institute, Cary, NC). Student's 2-tailed t-test or Mann-Whitney U-test was used for comparison of female control and #NOF group data.

Data are reported as the mean±standard deviation (SD) or as the median values [25th-75th percentiles]. Regression analysis was used to examine the relationship between measured parameters for the control and #NOF groups. The critical value for significance was chosen as $p<0.05$.

Results

Cancellous bone structural and turnover parameters in the #NOF and control groups. The structural parameters as well as indices of bone resorption and formation were measured. Table 1 presents the mean and median values for structural and bone turnover indices for intertrochanteric trabecular bone samples. Except for osteoid seam thickness (O.Th), which was increased in #NOF bone samples, there were no significant differences between the #NOF and age-matched control groups for any of these parameters.

The median values for the static indices of bone turnover, eroded surface and osteoid surface indices were not different between the #NOF and age-matched control groups (Table 1). Age dependency was detected for specific eroded surface (ES/BS) in the >65 year-old control group ($r=0.52$, $p<0.055$), although this parameter was not age-dependent in the younger control group nor the #NOF group (Figure 1A). When specific osteoid surface (OS/BS) was plotted as a function of age, the data for the >65 year-old control group correlated positively with age ($r=0.61$, $p<0.03$). OS/BS was not age-dependent for the >65 year-old #NOF group or the

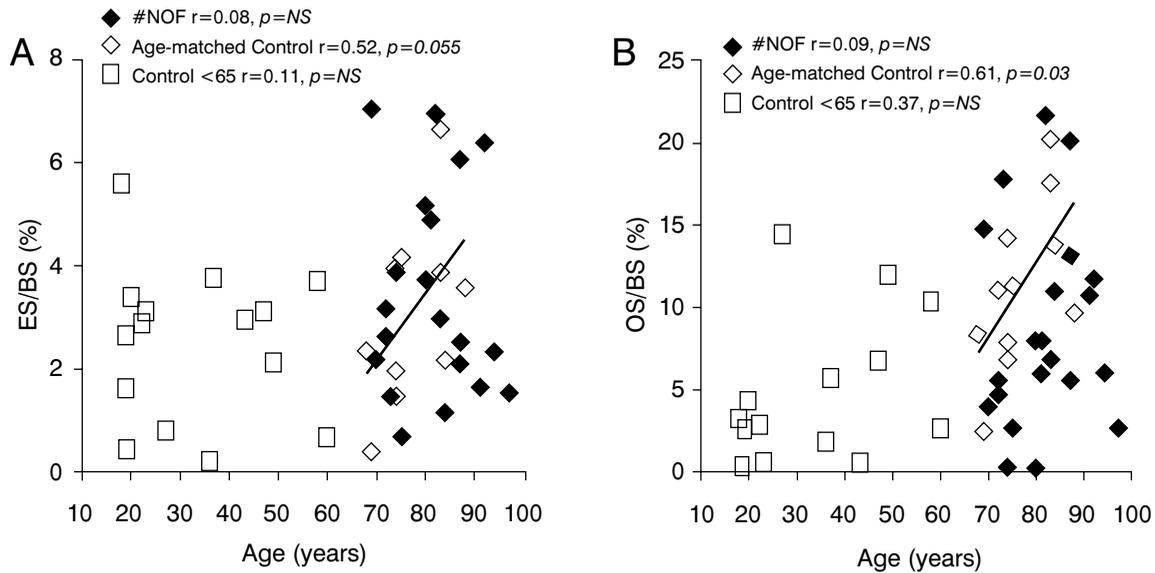


Figure 1. Static indices of bone turnover vs. age in trabecular bone samples from the intertrochanteric region of the proximal femur in female #NOF and female control groups. **A)** ES/BS vs. age in #NOFs (n=21; ES/BS=0.02*Age+5.0); age-matched controls (n=11; ES/BS=0.13*Age-7.1) and younger controls (n=15; ES/BS=-0.01*Age+2.8). **B)** OS/BS vs. age in #NOFs (n=21; OS/BS=0.07*Age+3.1); age-matched controls (n=11; OS/BS=0.46*Age-24) and younger controls (n=15; OS/BS=0.11*Age+1.2).

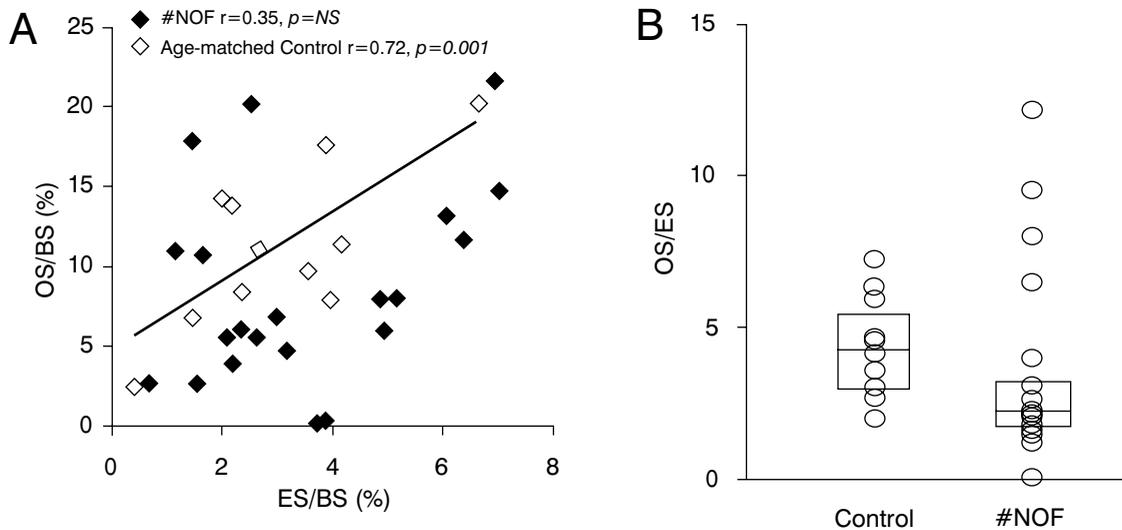


Figure 2. Relationships between the static indices of cancellous bone turnover in female #NOFs and age-matched female controls. **A)** ES/BS vs. OS/BS in #NOFs (n=21; OS/BS=1.2*ES/BS+4.9) and age-matched controls (n=11; OS/BS=2.2*ES/BS+4.7). **B)** OS/ES ratio in #NOFs (n=21; median [25th & 75th percentiles] 2.1 [1.6 - 3.1]) and age-matched controls (n=11; 4.2 [2.9-5.3]); $p<0.02$.

younger control group (Figure 1B).

Although not significant in the #NOFs, a positive relationship between ES/BS and OS/BS was detected in the >65-year-old control group (Figure 2A).

When these data were further interrogated by plotting the percentage osteoid surface to eroded surface quotient

(OS/ES) (Figure 2B), the OS/ES quotient was reduced in the #NOF group compared with the age-matched control group (4.2 [2.9-5.3] > 2.1[1.6-3.1], $p<0.02$). One interpretation of this finding is that formation is relatively reduced compared with resorption in the majority of patients who have sustained fragility fracture of the femoral neck.

Discussion

Rapid bone loss occurs in the early years after menopause followed by a significantly reduced rate of bone loss after the age of 65 years, 10 to 15 years after menopause¹⁵. At around the same age fracture rates, particularly of the hip, climb substantially¹⁶. To further understand the physical basis for fragility fracture of the femoral neck, we have measured histomorphometrically the structural and bone turnover indices for intertrochanteric trabecular bone samples from elderly female patients who have sustained a fractured neck of femur. We hypothesized that these parameters would be different from those of age- and sex-matched individuals without fracture. Given the difficulty of obtaining these samples, the study cohorts were not large; however, there were nevertheless at least two interesting findings from our study. Firstly, mean and median values of the measured bone structure and bone turnover histomorphometric parameters were not different between fracture and control subjects, although O.Th was significantly greater in the #NOF group. The O.Th is dependent on how much osteoid the osteoblasts produce, the rate of osteoid mineralisation, the lag time to the start of mineralisation following matrix formation and the extent to which osteoblasts enable mineralisation of the osteoid matrix. Our *in vitro* data suggest that osteoblasts in the fracture group have a reduced capacity to deposit a mineralised matrix (data not reported). Therefore, this can result in increased O.Th even in the presence of reduced bone formation. Further studies using fluorochrome markers to measure variables of dynamic bone formation are necessary to explore this issue further. Interestingly, this parameter was also increased in iliac biopsies in a group of male patients with idiopathic osteoporosis¹⁷, suggesting some common elements in male and female osteoporosis. Secondly, the median and range of the static indices of bone turnover were not significantly different between the two elderly (>65 years) female cohorts, #NOF and control groups. However, the >65-year-old control group showed significantly increased eroded surface (only ES/BV) and all measures of OS and OV were increased compared with the younger group of women (<65 years). Only the consideration of OS/ES showed a significant difference between #NOF and the >65-year-old control group. The decreased OS/ES in the #NOF group compared with the age-matched controls is consistent with a reported decrease in this parameter in idiopathic male osteoporotics (osteoporotics 1.6 versus controls 4.8)¹⁷. We interpret the difference in the median values for the OS/ES quotient between the #NOF and >65-year-old control samples (2.1 versus 4.2, respectively) to indicate a difference between the fracture and control groups with respect to relative amounts of bone resorption and/or formation surfaces. This imbalance of formation and resorption surface did not translate into a difference in BV/TV in the study groups. Bone quality, which may be captured by the proportion of formation to resorption surface, rather than bone quantity, may be influencing the risk to

fracture in this population. It is possible that differences in OS/ES eventually lead to weaker cancellous bone, which may be independent of the amount of cancellous bone. We report that formation surface is relatively reduced compared with resorption surface in the majority of patients who have sustained fragility fracture of the femoral neck. One possibility is that this imbalance of formation and resorption surface may influence bone adaptation². Though this study reports static indices of bone turnover, several authors have proposed that fracture risk in humans may be much better assessed by measuring parameters of bone turnover or bone adaptation rather than referring to BMD measurements^{17,18}.

A recent study by Kobayashi et al.⁸, has reported histological evidence of trabecular bone modeling in iliac crest bone from patients with osteoarthritis. Although the prevailing view still is that trabecular bone modeling does not persist into adulthood, it is interesting to consider that contributors to OS/BS may be both bone remodeling and bone modeling. Periosteal bone expansion and trabecular expansion, driven by bone modeling, is currently recognized as a significant factor in reshaping the skeleton of the aged^{8,18}. The decrease in OS/ES in both our #NOF group and the idiopathic male osteoporotic study cited above, allow the possibility that bone modeling may be attenuated in cases with bone fragility¹⁷.

The recent literature suggests that an increased rate of bone turnover with a relative reduction in bone formation may be an important mechanism for reducing bone strength below the fracture threshold^{19,21}. OS/ES is a ratio that can change as a result of a change in OS or ES or coupled changes in OS and ES. We hypothesise that increased activation frequency will change ES and/or OS. The absolute changes that can occur in OS and ES, depending on whether the changes are independent or coupled changes, may or may not change the OS/ES ratio. In the context of these reports our finding of decreased OS/ES is consistent with a difference in bone turnover associated with a relative reduction in bone formation surface and/or down regulation of bone formation surface associated with bone modeling.

In summary, the data presented here indicate that perturbations in bone formation surface are potentially important in producing bone in the proximal femur with increased propensity to fracture. These data also support the concept that trabecular bone modeling may be a factor influencing bone strength in addition to bone mass. The relative reduction in bone formation surface and/or down regulation of bone formation surface without an accompanying change in bone volume can help to explain why an individual does or does not fracture.

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