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Bone mineral and geometric changes through the femur with immobilization due to spinal cord injury

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Abstract—This cross-sectional study describes bone mineral and geometric properties of the midshaft and distal femur in a control population and examines effects of immobilization due to spinal cord injury (SCI) at these skeletal sites. The subject populations were comprised of 118 ambulatory adults (59 men and 59 women) and 246 individuals with SCI (239 men and 7 women); 30 of these were considered to have acute injury (SCI duration <1 year). Bone mineral density (BMD) was assessed at the femoral neck, and midshaft and distal femur by dual energy absorptiometry. Geometric properties, specifically cortical area, polar moment of inertia, and polar section modulus, were estimated at the midshaft from cortical dimensions obtained by concurrent radiography. Reduction in BMD was noted in all femoral regions (27%, 25%, and 43% for femoral neck, midshaft, and distal femur, respectively) compared with controls. In contrast, although endosteal diameter was enlarged, geometric properties were not significantly reduced in the midshaft attributable to the age-related increase in periosteal diameter. These results suggest that simultaneous assessment of bone mineral and geometric properties may improve clinically relevant evaluation of skeletal status.

Key words: *bone mineral density, DXA, femur, osteoporosis, spinal cord injury.*

INTRODUCTION

Osteopenia following paralysis or partial immobilization has been documented in individuals with spinal cord injury (SCI), stroke, and nonparalytic medical conditions, as well as in studies of humans voluntarily participating in extended bedrest (1). The bone loss resulting from elimination of habitual mechanical loading is region specific and associated with the degree of immobilization. In the past decade, densitometry has been increasingly used to document these degenerative changes after SCI. Most of the published studies have reported changes in bone mass of the hip, the standard densitometric measurement site, and several reports are available of changes in total leg bone mass, determined from whole body densitometry, as well as changes in tibia bone mass. While much has been learned about skeletal response to paralysis from these studies, the util-

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ity of these data for assessing specific fracture risk is limited. The majority of nontraumatic fractures in individuals with SCI occur in the femoral diaphysis and distal femur (2–7), and there is only one prior report of bone response in these regions (8). Accurate determination of fracture risk should be based on regional change in bone mass, as has been demonstrated in numerous studies of hip fracture prediction (9–14).

Bone mass, expressed as bone mineral content (BMC) and bone mineral density (BMD), has been shown to correlate with breaking strength of bone (15–20). As a result, BMD is commonly equated with bone strength in clinical prediction of fracture risk. However, this is an incomplete association, as both material (i.e., bone mineral content) and geometric properties determine bone mechanical strength and resistance to failure (fracture). Geometric properties, moment of inertia and section modulus, reflect both the amount and distribution of tissue in cortical bone and correlate better with breaking strength than bone mineral properties alone. Particularly in skeletal regions which are primarily cortical (i.e., the femoral midshaft), geometry may be an overriding factor in determining bone strength. Thus, while bone mass alone does not fully discriminate those who will fracture from those who will not, incorporation of geometry in clinical evaluation of skeletal status has been shown to enhance prediction of fracture risk (21,22).

The cortical femoral diaphysis approximates a cylindrical beam, and its geometric properties can be calculated from measurements of cortical dimensions to provide estimates of bone strength in addition to those derived from bone mineral measurements. In a recent study of fracture morphology (unpublished data), we found that a significant number of femoral fractures in individuals with SCI are spiral, a pattern that is associated with torsional loads. Therefore, geometric properties that describe the bone's strength in torsion–polar moment of inertia and polar section modulus–are the most appropriate for understanding fracture risk for these individuals in this region. There are no prior studies that examine these properties in a human population study, and none with specific focus on individuals with SCI.

This cross-sectional study was designed with several objectives: a) to describe bone mineral properties throughout the femur and geometric properties at the femoral midshaft in an ambulatory reference population and to investigate b) the influence of gender and age and c) the effect of acute and chronic immobilization on these properties at these skeletal sites.

METHODS

Subject Population

Two hundred and forty-six healthy adults with SCI, aged 21 to 78, were recruited from the patient census of the VA Palo Alto SCI Center. Reflective of the gender distribution within the VA, especially of those with SCI, the overwhelming majority (239) of these individuals were male. There were approximately even numbers of subjects with paraplegia (131) and tetraplegia (115), and the duration of their SCI ranged from 0.1 to 51 years. In addition, 118 healthy ambulatory control subjects were recruited from the Stanford and local Palo Alto communities. These included 59 men and 59 women ranging in age from 19 to 83 years. Although females account for only 18 percent of SCI cases in the general population (23) and only 1.5 percent in the VA Palo Alto SCI Center population, both male and female controls were sought in order to explore gender differences in bone mineral and geometric properties in these novel measurement sites, and to provide suitable comparison values for women with SCI. Demographic information for the SCI and reference populations is summarized in **Table 1**.

Femoral Measurements

Dual x-ray absorptiometry (DXA; Hologic QDR 1000/W; Bedford, MA) was used to determine BMC (g/cm) and BMD (g/cm^2; BMC divided by the projected area) of the proximal, midshaft, and distal femur. Proximal femur bone mass was measured by standard methodology, which involves placement of a 15-mm region of interest on the femoral neck. Midshaft and distal femur measurements were made from a single scan originating at the femoral condyles using the spine acquisition software; as these are novel measurement sites, no regional DXA programs are available (**Figure 1, (a)**). Bone mass of the femoral midshaft was determined at a 10-mm section approximating the midpoint, based on stature-estimated bone lengths (Mildred-Trotter formula; 24); this was done to reduce anthropometric measurement error and provide reliable repositioning. Distal femur bone mass was determined at a 15-mm section immediately above the patella. Standard DXA assessment of the cancellous femoral neck uses a 15-mm section, so we defined an equivalent size region at the cancellous distal femur; other studies of the cortical midshaft femur have used a 10-mm section at this site. Cortical dimensions of the femoral midshaft were measured from radiographs obtained concurrently with DXA

Table 1.
Physical characteristics of the reference and SCI populations. Summary values are presented as mean±SD (range).

	Ambulatory		Chronic SCI[a]		Acute SCI[b]	
	Male	Female	Male	Female	Male	Female
Number	59	59	210	6	29	1
Age	38.4±13.9 (19-73)	45.8*±17.5 (21-83)	49.5*±12.6 (21-78)	41.2±16.8 (22-67)	43.5±18.5 (19-81)	24.1
Weight	76.2±10.8 (54.9-108.9)	62.1±9.6 (47.6-90.7)	80.4±15.0 (43.5-145.1)	67.9±17.9 (52.1-99.8)	74.5±14.2 (47.5-102.1)	68.5
BMI	24.3±3.0 (20-32)	23.0±3.5 (18-35)	24.7±4.4 (16-41)	25.4±8.1 (19-40)	23.7±3.9 (15-32)	26.0
Duration	na	na	17.1±11.9 (2-51)	15.2±15.7 (2-46)	0.5±0.3 (0.1-1.2)	0.5

[a]Duration of SCI > 1 year; [b] Duration of SCI 1 year or less; *=Significantly different from ambulatory males, $p<0.05$; age and duration in years; weight in kg; BMI=Body Mass Index, in kg/m^2; na=not applicable.

by placement of an x-ray cassette over the thigh during the scan (**Figure 1, (b)**). Although the image has reduced resolution, this approach eliminates the magnification error present with standard radiography. Measurements included mediolateral outer diameter (OD), medial and lateral cortical thicknesses, and mediolateral inner diameter (ID). Bone mineral and geometric properties were obtained on the left limb for most individuals, but the right limb was used when the left could not be measured. Data were unavailable at some sites in some individuals due to heterotopic ossification at the measurement site, fracture or orthopedic instrumentation, joint contracture preventing proper limb positioning, or extremely low bone mass.

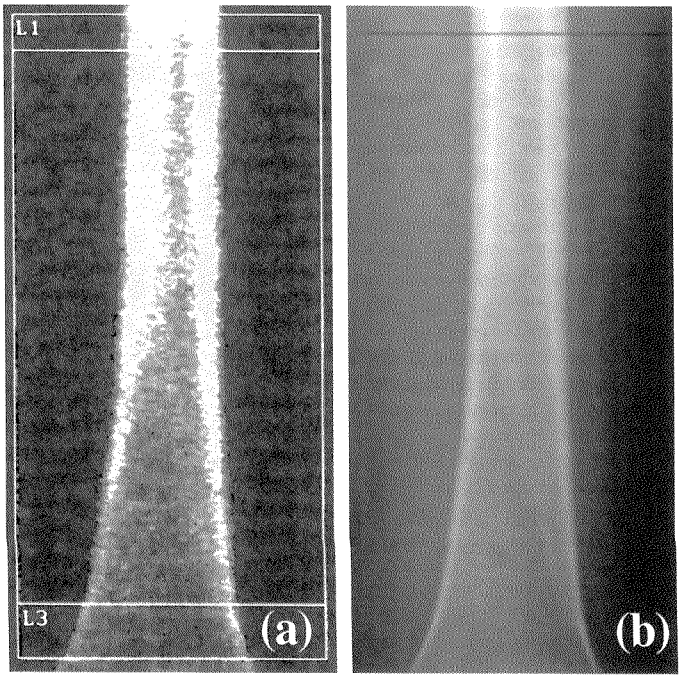

Figure 1.
DXA (a) and radiographic (b) images of the midshaft and distal femoral measurement sites.

Determination of Geometric Properties

Geometric properties–cortical area (CA, cm^2), polar moment of inertia (J, cm^4), and section polar modulus (ZJ, cm^3)–were derived for the femoral midshaft based on radiographic measurements, modeling the midshaft as a beam and the cross section as a concentric annulus. These geometric properties represent the bone's resistance to torsional loading, assuming it is homogenous, isotropic, and behaves in a linear elastic manner. While bone, in general, does not satisfy these conditions, nonetheless these properties provide an adequate estimation of its torsional strength. Moreover, CA, J, and ZJ are a function only of the inner and outer diameters; as such, they are purely geometric properties that do not consider the density of mineral within the tissue.

$$CA=\pi\frac{(OD^2-ID^2)}{4}$$

$$J=2\pi\frac{(OD^4-ID^4)}{64}$$

$$Z_J=\frac{J}{0.5(OD)}$$

Statistical Analyses

Femoral data were initially evaluated for gender and age effects in ambulatory control subjects by analysis of variance and covariance and by linear regression analysis. Changes in femoral bone and geometric properties with acute paralysis were assessed by linear regression analysis in a subsample of 30 individuals with SCI of 1 yr duration or less. Rates of change for each site were estimated from the slope and y-intercept, taken to represent the initial bone mass and incremental change, respectively. Evaluation of the effect of chronic immobilization at these femoral sites excluded subjects with acute SCI (duration <1 yr). Comparisons were made by unpaired t-test with data from ambulatory control subjects. Because the lower mean age of the male control group would confound evaluation of the effect of immobilization on bone properties, younger control subjects were excluded from these analyses such that the age distributions of the ambulatory and SCI populations were equivalent. Changes in bone and geometric properties in subjects with SCI attributable to age were examined by linear regression analysis.

RESULTS

Femoral Values in Ambulatory Subjects

Initially, we evaluated whether our sample of ambulatory controls was representative of the general population by examining their femoral neck Z-scores; Z-scores represent the deviation of each individual's BMD values from the mean of age-adjusted normative data (based on the manufacturer's reference database). The Z-scores of control subjects of both sexes were not different from zero, indicating normal bone mass for age.

Summary values for bone mineral (**Table 2**) and geometric properties (**Table 3**) are presented for male and female control subjects. For all bone parameters except midshaft ID, female values are lower than male values on average, although there is considerable overlap, especially in the femoral neck. There are moderate to good associations between BMD of the three femoral regions (**Table 4**). The weakest correlation is between proximal and midshaft femur BMD, and distal femur BMD is similarly correlated with both midshaft and proximal femur BMD. While the amount of mineral (BMC) is often taken as an estimate of the cortical area of the region scanned, this only holds true if the mineral density and porosity are constant. Midshaft BMC is only moderately correlated with cortical area (**Figure 2**), which demonstrates the difference in these two quantitative measures. Thus, BMC captures the total mineral amount in the section of bone scanned, but provides no information about how the tissue is distributed, and cortical area provides no information about the density of mineral or porosity of tissue.

Table 2.
Bone mineral density (BMD) in three femoral regions: reference values for ambulatory controls by gender.

Region	Males	Females
Neck	0.887±0.133	0.774*±0.116
	(0.64-1.33)	(0.55-1.02)
Midshaft	1.975±0.207	1.676*±0.180
	(1.11-2.34)	(1.25-2.01)
Distal	1.008±0.156	0.800*±0.151
	(0.62-1.27)	(0.26-1.08)

Mean±standard deviation, and (range); BMD in g/cm2; *=significantly different, p<0.0001.

Table 3.
Geometric properties of the femoral midshaft: reference values for ambulatory controls by gender.

Property	Males	Females
OD	2.718±0.198	2.432+±0.400
	(2.35-3.10)	(2.10-3.13)
ID	1.111±0.195	1.063±0.238
	(0.78-1.57)	(1.25-2.01)
CA	4.834±0.764	3.839*±0.903
	(3.39-6.30)	(2.74-6.17)
J	5.346±1.530	3.658*±1.608
	(2.85-8.81)	(1.87-8.76)
Z_J	3.875±0.837	2.933*±0.864
	(2.43-5.68)	(1.79-5.65)

Mean±standard deviation, and (range); OD=outer diameter, in cm; ID= inner diameter, in cm; CA=cortical area, in cm^2; J=polar moment, in cm^4; Z_J=section polar moment, in cm^3; +=significantly different, p<0.005; *significantly different, p<0.0001.

Table 4.
Associations between femoral regions: matrix of bone mineral density (BMD) correlation coefficients (r) for ambulatory controls, both genders (n=118).

	Neck	Midshaft	Distal
Neck	1.00	--	--
Midshaft	0.64	1.00	--
Distal	0.76	0.78	1.00

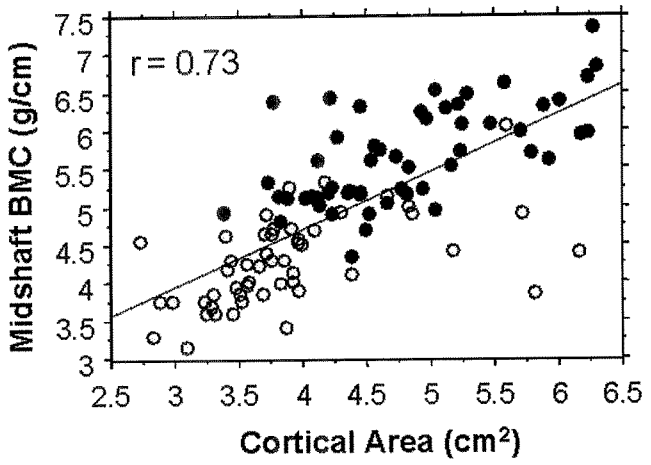

Figure 2.
Association between midshaft bone mineral content (BMC) determined by densitometry and cortical area determined from radiographic measurements. Open circles represent ambulatory control females (n=59) and closed circles represent ambulatory control males (n=59).

There are moderate correlations between age and BMD for the three femoral sites but no evidence of an association between age and geometric properties (r values below 2.0). Bone mass declines with age at similar rates for male and female subjects in the femoral neck (0.004 g/cm²/yr for both) and distal femur sites (0.003 and 0.004 g/cm²/yr), but the age-related decrement is three times greater in females than in males in femoral midshaft BMD (0.006 *versus* 0.002 g/cm²/yr). These rates of change translate to between 0.1 percent and 0.5 percent per yr.

Changes in Femoral Bone Mass and Geometry Following Acute SCI

Rapid bone loss is suggested for all three femoral sites in the first year after SCI. During this time, BMD is reduced 21 percent (-0.194 g/cm²>) in the femoral neck, 17 percent (-0.346 g/cm²) in the femoral midshaft, and 25 percent (-0.260 g/cm²) in the distal femur, estimated from regression analysis of cross-sectional data. Slight expansion of the ID of the midshaft is also observed in the first year post-SCI, +7 percent (0.8 mm/year). In the next 5 years, the loss rate is much less in the femoral neck and midshaft, 0.016 and 0.033 g/cm² per year, respectively–less than 2 percent/year. Lesser decrements were observed in cortical area, J, and ZJ (-7, -10, and -9 percent, respectively), and no change was noted in OD. Bone loss in the distal femur is also less, but not negligible, through this period at a rate of 0.058 g/cm² per year–approximately 6 percent/year. Expansion of the ID of the femoral midshaft continues at essentially the same rate as the first year of paralysis (0.9 mm/year), +8 percent/year. Finally, over the 5 years post-injury, there are slight increments in OD, cortical area, J, and ZJ (between 1 and 3 percent per year).

Effect of Chronic SCI on Femoral Bone Mineral and Geometric Properties

Throughout the femur, bone mass is significantly reduced as a result of paralysis (**Figure 3**). There are no differences between individuals with paraplegia and tetraplegia in any bone parameters. In men with chronic SCI, femoral neck BMD is 27 percent lower, midshaft BMD is 25 percent lower, and distal femur BMD is 43 percent lower than ambulatory controls. Expansion is observed in the ID of the femoral midshaft (27 percent) but not the OD, and cortical area is reduced by 15 percent; there are no differences in midshaft J or ZJ in men with chronic SCI compared with ambulatory men (**Figure 4**). Similar changes are observed for females with SCI compared with female controls, except for a slightly lower decrement in femoral neck BMD (-20 percent) and a greater increase in the ID of the femoral midshaft (+40 percent).

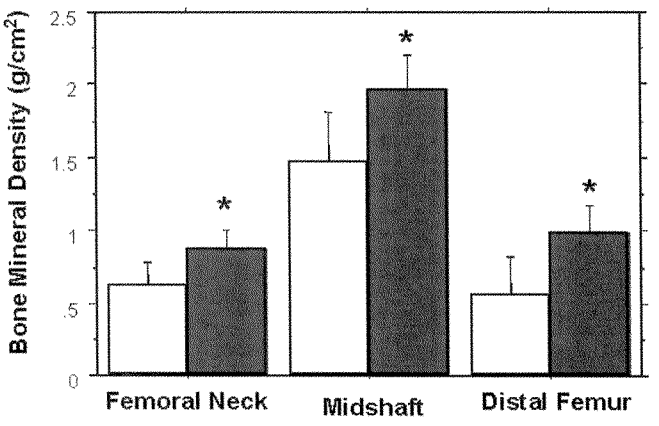

Figure 3.
Bone mineral density in three femoral regions: Comparisons between ambulatory and SCI subjects. Summary values, mean and standard deviations, are presented for the males subjects only, excluding subjects with SCI of less than one year. Values for ambulatory subjects are shown as dark bars (n=37); values for SCI subjects are shown as white bars (n=214). Significant differences ($p<0.0001$) between groups are denoted by asterisk.

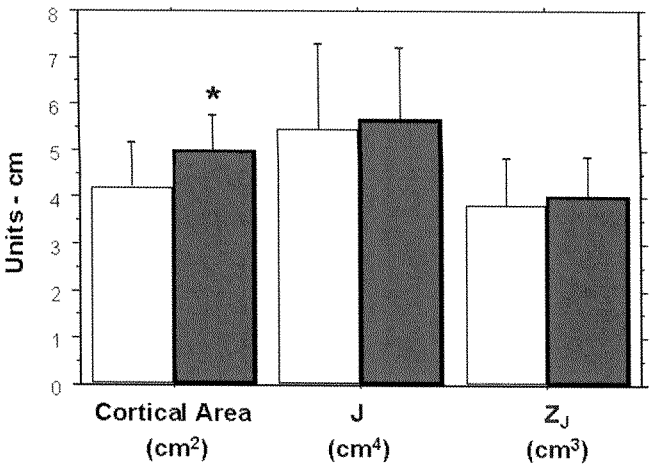

Figure 4.
Geometric properties of the femoral midshaft: Comparisons between ambulatory and SCI subjects. Summary values, mean and standard deviations, are presented for the males subjects only, excluding subjects with SCI of less than one year duration. Values for ambulatory subjects are shown as dark bars (n=37); values for SCI subjects are shown as white bars (n=214). Significant differences ($p<0.0001$) between groups are denoted by asterisk.

In both ambulatory subjects and those with SCI, a slow rate of loss is observed in BMD with aging. Although the variance in the data is high, resulting in low regression coefficients, there are significant effects of age and/or duration of SCI on BMD (**Figure 5**). The rate of bone loss does not differ between ambulatory and SCI subject populations for the femoral neck and is slightly lower in subjects with SCI in the distal femur (-0.001 *versus* -0.003 g/cm^2 per year). Midshaft bone loss is fourfold greater in subjects with SCI compared with ambulatory control subjects (-0.008 *versus* -0.002 g/cm^2 per year), but this rate of loss translates to less than 0.5 percent change per year. While there is no significant difference in mean OD of the femoral midshaft between the groups, a slightly greater rate of expansion is observed with increasing age in subjects with SCI (+0.04 mm per year) than in ambulatory subjects (+0.01 mm per year). Slight increases with age are observed for all three geometric properties, but the rates are not different between subject groups, and the large population variance prevents these effects from being significant.

DISCUSSION

In this paper, we provide reference data describing bone mineral properties of the midshaft and distal femur

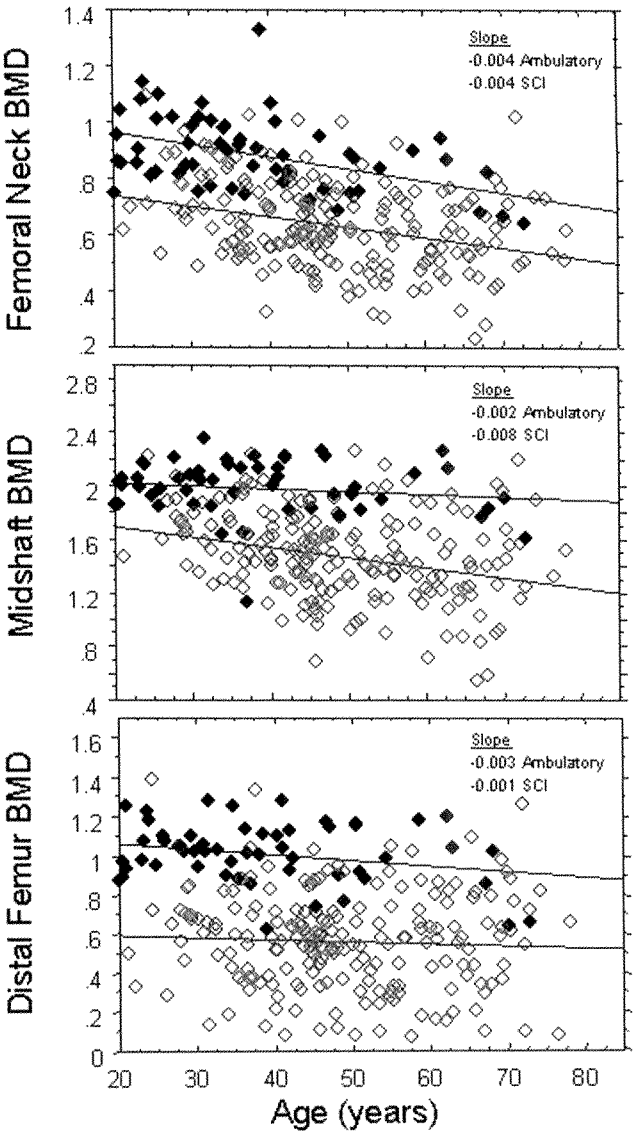

Figure 5.
Effect on bone mineral density in the femoral neck (a), femoral midshaft (b), and distal femur (c): Comparisons between ambulatory and SCI subjects. Data are presented only for male subjects and exclude subjects with SCI of less than 1 year duration. Values for ambulatory subjects are shown as closed diamonds (n=59); values for SCI subjects are shown as open diamonds (n=214).

and estimations of geometric properties (J and ZJ) of the femoral midshaft with respect to failure in torsion. Examination of femoral neck Z-scores for BMD indicates that both male and female ambulatory controls can be considered representative of the general population. In addition, estimates of femoral midshaft BMC for young ambulatory males and females are similar to those reported elsewhere (25), although the measurements were made

from whole body densitometry and not a region-specific scan.

In the ambulatory reference population, bone mass values were lower in females than in males for all three femoral sites with a slightly greater reduction seen in the distal femur (-21 percent, compared with -13 percent and -15 percent in the femoral neck and midshaft, respectively). The more dramatic difference observed in geometric properties of the midshaft (21, 32, and 24 percent reduction in cortical area, polar moment of inertia, and polar section modulus, respectively) demonstrate the importance of considering bone size and shape as well as bone mass when evaluating bone strength. As has been demonstrated previously (26), there is an age-related expansion of the femoral cortex in men but not in women. This larger cortex constitutes an increase in moment of inertia and section modulus, and thus counteracts some of the reduction in structural strength attributable to the loss of mineral with aging. In addition to the amount of bone mineral present, other material properties that contribute to bone strength include true mineral density of the bone tissue and bone porosity. The moderate association between BMC and cortical area (**Figure 2**) can be explained by nonuniformity in these properties, not accounted for by either measurement. Bone shape and size, mineral content and distribution, and porosity contribute to differences between men and women in bone mineral and geometric properties.

Rapid bone loss in the first year following acute SCI occurs in the proximal femur, consistent with prior reports (8,27,28), accompanied by significant loss in the diaphyseal and distal regions. The loss in bone mass is greater in the cancellous bone sites (femoral neck and distal femur) than in the cortical midshaft during the first year. The endosteal diameter begins to expand and a corresponding decrease is seen in the cortical area of the midshaft, but little change is noted in either polar moment of inertia or polar section modulus in the first year, as there is no significant change in the outer cortex. Thus, the rapid reduction in bone tissue mass following acute paralysis is not immediately reflected in a change in geometric properties.

Long-term bone mineral loss due to paralysis is much greater in the distal femur than in the proximal femur or femoral midshaft. This greater decrement in the distal region is consistent with the more rapid initial rate of loss observed in the first year and the continued loss observed in the subsequent five years, when bone loss in the midshaft and proximal regions appears to subside. An explanation for this discrepancy is that the greater bone loss in the distal femur may represent a greater degree of unloading of the knee than of the hip: that is, the proximal femur may be somewhat protected by residual loading by the upper body during wheelchair sitting. Further, cancellous bone may be more reactive than cortical bone to alteration in the mechanical environment. These suggestions are consistent with evidence from other studies demonstrating similar reduction in proximal femur BMD (14–28 percent) and increasingly greater reduction in bone in the proximal and distal tibia (26–50 percent) with evidence of greater decrement in cancellous compared with cortical bone (8,27,29–31). There appears to be a gradient of response through the lower limb which might reflect the magnitude of the (previous) habitual loading history, in that bone loss may occur relative to the differential reduction in loading from pre- to post-SCI loading. That is, the reduction in mechanical stimulus is greatest in skeletal regions that were previously exposed to greater loads during walking and normal activity, compared with those where the loads were lesser (more distal versus more proximal sites), and bone loss may be greatest in regions where the reduction in mechanical loading is greatest.

A different picture emerges with consideration of the geometric properties. While the midshaft ID is significantly larger in men with long-term SCI compared with reference values, the OD, polar moment of inertia, and polar section modulus are not different. The explanation for this lack of difference is that a) the outer diameter expands with age regardless of mechanical environment and thus demonstrates no negative effect attributable to immobilization and b) because the OD term dominates in the calculation of J and ZJ, the expansion of the ID has a negligible influence on these properties. Thus, in the absence of essential changes in material or structural properties, reduction in bone strength might not be expected based on geometry alone. A similar finding is reported in a study of excised tibias from persons with longstanding SCI mechanically tested in torsion (32). Although reduction in cortical thickness and cortical area is reported compared with ambulatory control tibias, no reduction in polar moment of inertia is observed. This emphasizes the need to consider material properties (i.e., bone mineral) and geometric properties simultaneously when evaluating structural strength.

After the initial rapid decline, bone mineral loss observed in the femoral neck and distal femur appears to be due to aging rather than chronic immobilization,

although there may be a continued reduction in bone mass in the femoral midshaft attributable to duration of injury. Because of the large variance in these data in both ambulatory and SCI subject populations, it is difficult to discern with any certainty age or duration trends in these cross-sectional data. Further, any analysis exploring the effect of duration of SCI is complicated by the age of the individual at the time of SCI as well as the normal aging process prior to and following the SCI. While most prior cross-sectional studies have not demonstrated bone loss ongoing with chronic immobilization (8,31,33–36), several studies suggest the opposite (29,30,37,38).

One of the limitations of this study is the relatively small size of the reference population and the skew towards younger subjects in the male control group. While we feel confident that the control population is reasonably representative of the population at large and that the comparisons discussed here are also reasonable, it might be necessary to recruit a broader population sample for more in depth investigation of the contributing factors of body habitus and mass, habitual loading history and activity level, and age on bone mineral and geometric properties of the midshaft and distal femur. Another limitation is that the rates of change presented for the acute period following SCI are approximations derived from regression analysis of cross-sectional data. However, as the rate of loss reported for the femoral neck is similar to previous reports, and for each site the intercept is nearly equal to the mean BMD for 20- to 30-year-old male controls, we feel that these estimates of rate of change are plausible. Finally, although cross-sectional data can never replace longitudinal data for determination of true changes with time, the data reported here, for individuals with duration of SCI as long as 50 years, provide an overview of the population effects of long-term immobilization that would not be possible to access longitudinally.

In this study, we have begun to explore the bone response to SCI and immobilization in the regions of the femur that are most susceptible to bone failure. In order to improve clinical evaluation of bone health and provide accurate estimation of fracture risk in individuals with SCI, it will be necessary to develop region-specific normative data for the midshaft and distal femur bone properties and to define the factors that contribute to or protect against bone loss at these sites. Assessment of both bone mineral and geometric properties appears to be essential to properly understand of how bone responds to both acute and chronic immobilization, and to reliably determine bone strength and fracture risk in these individuals.

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