Bone Impairment and Spinal Cord Injury

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Pathologic fractures alerted the clinician of bone loss secondary to spinal cord injury (SCI) in the early twentieth century. At mid century bone biopsies from the pelvis and chemical markers, mostly from the urine, began to define this phenomenon. By century's end newer technologies such as densiphotometry, computed tomography and absorptiometries allowed identification of locations as well as specific amounts of bone loss.

Characterization of bone loss or loss of bone mineral density (BMD) in persons with SCI remains problematic at the beginning of this century due in large part to the relatively small population of individuals with SCI from which research samples can be drawn. Duration of injury (DOI), sex, neurologic classification, age and acute versus chronic loss have been confounding variables in defining this bone loss. This entity is not systemic. A consensus has not established the most appropriate study site. Studying data in men with neurologically complete SCI reduces the influence of some of the confounding variables, such as estrogen, variable sensory feedback and voluntary muscle influence. BMD at the knee may be selected as an effective site to study treatment since fractures herein are common. Knowledge of the natural history of bone loss, sites of loss, risk factors and fracture sites will assist in research design and outcome interpretation of treatments.

Natural History of Bone Loss

Changes in BMD have been divided into three phases: acute (or response to injury); sub-acute (or adaptation and adjustment); and chronic (Garland et al. 1992, Garland et al. 2005a) (Figure 1).

Acute (Response to Injury) Phase

This phase begins immediately after SCI and lasts approximately four months. BMD "weekly" changes are: (-) 0.5% for the lumbar spine, (-) 2% for the pelvis, os calcis and entire lower extremity (LE) total bone mineral (TBM); (-) 0.75% for the hip; (-) 1% for the knee, both distal femur and proximal tibia (Garland et al. 1992, Garland and Adkins

2001, Garland et al. 2005a) (Figure 2). Bone resorption markers in the urine and serum become elevated soon after injury and peak approximately 24 weeks after injury (Roberts et al. 1998, Warden et al. 2002, Maimon et al. 2005). Bone building markers are either minimally or not elevated. This phase is largely osteoclastic with negligible osteoblastic effects.

Sub-Acute (Adaptation and Adjustment) Phase

This phase persists for twelve months or so. Bone loss at the lumbar spine is already stabilizing. BMD "monthly", as opposed to acute phase "weekly" changes are: (-) 2% at the pelvis, os calcis and LE (TBM); (-) .75% at the hip; (-) 1% at the knee (Garland et al. 1992, Chow et al. 1996, Garland et al. 2004a) (Figure 3). Many of the bone resorption markers have or are returning to normalcy. Endocrine markers, such parathyroid (PTH), may become elevated at the beginning of this phase in response to acute phase changes but are returning to baseline by the end of this phase (Chen and Stein. 2003).

Chronic Phase

The chronic phase begins approximately two years or so after injury. The lumbar spine has stopped losing bone, may have a period of stability and then begins to gain BMD. The LE (TBM) and os calcis (BMD) lose (-) 1% annually. Although the annual trend is (-) 1% decrease in LE TBM, some LE may demonstrate a positive annual gain. The hip BMD remains relatively stable with some individuals gaining while others lose BMD. The knee BMD decreases (-) 1% annually but one third of men with paraplegia may show an increase (Garland et al. 2008) (Figure 4). Bone and endocrine markers are normal.

The bone changes in the various phases can be summarized as the following. The amount of bone loss below the pelvis progressively increases from the hip to the os calcis. The lumbar spine loses (-) 10% BMD or so acutely, stabilizes sub-acutely and gains bone chronically such that its BMD values may eventually equal or surpass young able bodied values. The etiology of this gain is unknown. The hip BMD decreases approximately (-) 20-25% acutely and subacutely (near its fracture threshold, see discussion below) but chronically remains relatively stable with hip BMDs increasing in some and decreasing in others. This increase in hip BMD in some men with paraplegia may be due to the same mechanism that increase lumbar spine BMD. The hip loss may continue in men with tetraplegia and women with neurologically complete injuries without periodic gains. The knee rapidly loses BMD acutely, slows sub-acutely decreasing by a total of 25-30% in men with complete injuries and 30-40% in women with complete injuries at 1.5 -2 years after injury. Chronically the knee BMD continues a downward trend at (-) 1% annually in women with complete injuries and men with complete tetraplegia, although some men with complete paraplegia may gain BMD. The pelvis and os calcis BMD and LE – TBM decrease rapidly over the early phases to a (-) 40-50% decrease but then appear to stabilize.

Risk factors

Risk factors support understanding the etiology of a disease, classification, prevention and effectiveness of interventions. Many risk factors are modifiable but SCI introduces

additional non-modifiable elements such as neurologic injury (complete versus incomplete), level of injury, age at injury and duration of injury. SCI osteoporosis is inappropriately classified as immobilization. SCI bone loss is much greater than the (-) 10% loss from immobility. Immobility implies that mobility will cure this entity. To date studies fail to support standing or walking as an effective means of increasing LE BMD (Craven et al. 2008).

Neurologic Insult

Completeness of injury is the strongest indicator of decreased BMD in the LE (Garland et al. 2001a, Garland et al. 2004b, Garland et al. 2005b). This risk factor is so strong it may negate many other modifiable risk factors identified in the able bodied. Incomplete lesions result in decreases of (-) 15-25% BMD at the knee, depending on the muscle strength (Garland et al. 1994) (Figure 5). The loss in both neurologic groups is much greater than that of immobilization.

Sex

The small number of women with SCI limits knowledge of their bone loss (Garland et al. 2001a, Garland et al. 2001b, Garland et al. 2004b, Garland et al. 2005b, Garland et al. 2008). Women with SCI were divided into three groups: < 30 years; 31-50 years; > 50 years (Garland et al. 2001b). Each group was comprised of nearly equal numbers of women with complete injuries and able-bodied women controls. BMD values between the SCI versus control groups are noted in Table 1. Age normalized Z scores are detailed in Table 2.

Table 1

	Knee	Hip	Spine
Age > 50 years			
Comparison			
Mean and Standard Deviation	.083 ± 0.09	.051 ± 0.14	0.88 ± 0.14
Adjusted Mean*	0.83	0.51	0.88
Spinal Cord Injury			
Mean and Standard Deviation	.045 ± 0.12	.039 ± 0.18	1.02 ± 0.14
Adjusted Mean*	0.44	0.38	1.01
Age 31-50 years			
Comparison			
Mean and Standard Deviation	.093 ± 0.18	.074 ± 0.25	1.02 ± 0.17
Adjusted Mean*	0.92	0.72	0.99
Spinal Cord Injury			
Mean and Standard Deviation	.052 ± 0.13	.052 ± 0.11	1.05 ± 0.15
Adjusted Mean*	0.54	0.54	1.07
Age ≤ 30 years			
Comparison			
Mean and Standard Deviation	.095 ± 0.18	.080 ± 0.09	1.02 ± 0.11
Adjusted Mean*	0.95	0.80	1.01
Spinal Cord Injury			
Mean and Standard Deviation	.058 ± 0.11	.065 ± 0.15	.097 ± 0.22
Adjusted Mean*	0.59	0.66	0.99

*adjusted for individuals' weights.

Table 2

	Hip	Spine
Age > 50 years		
Comparison		
Mean	-0.42	-0.34
Adjusted Mean*	-0.39	-0.28
Spinal Cord Injury		
Mean	-1.14	1.31
Adjusted Mean*	-1.24	1.14
Age 31-50 years		
Comparison		
Mean	1.01	0.34
Adjusted Mean*	0.86	0.08
Spinal Cord Injury		
Mean	-1.33	0.52
Adjusted Mean*	-1.17	0.77
Age ≤ 30 years		
Comparison		
Mean	0.33	0.47
Adjusted Mean*	0.27	0.37
Spinal Cord Injury		
Mean	-1.13	-0.53
Adjusted Mean*	-1.10	-0.31

*adjusted for individuals' weights.

BMD of the lumbar spine decreased (-) 2% in SCI Group I (< 30 years) but increased (+) 8% and (+) 15% respectively in SCI Groups II (31-50 years) and III (> 50 years) when compared to controls. SCI Group III had lumbar BMD values equal to the youngest able-bodied controls, Group I. SCI Group I had a negative Z score but the older two SCI Groups had positive Z scores.

The mean hip BMD values decreased (-) 18%, (-) 25% and (-) 25% respectively between the SCI groups compared to control groups. The mean Z scores, however, were nearly equal in all SCI groups at (-) 1.

The mean knee BMD values decreased (-) 38%, (-) 41% and (-) 47% between the SCI groups compared to the controls. The decrease in BMD from young controls (Group I) to aged SCI (Group III) was (-) 53%. These decreases in BMD were greater than the decreases in the men with complete injuries (Garland et al. 1992, Garland et al. 2004a).

Body Mass Index (BMI)

An above average BMI has a positive relationship with BMD in the post-menopausal population. Possible mechanisms include: more adipose tissue which converts androstanedione to metabolically active estrogen; weight bearing bones subject to more loading; higher peak bone mass in adolescence (Felson et al. 1993, Tremolliers et al. 1993).

Reports evaluating BMI's influence on BMD in men with SCI identified the following. High BMI (>25kg/m^2) positively influences the spine, hip and especially the knee and is a reliable predictor (after completeness and sex) of positive BMD increase (Garland et al. 2001a, Garland et al. 2001b, Garland et al. 2004b, Garland et al. 2005b). The previously mentioned mechanisms of this increase in the able-bodied are, however, probably not valid herein. The SCI population begets more adipose tissue and less muscle but these studies were in men negating the estrogen effect. Minimal, if any, weight bearing had been present. A high pre-SCI BMI affects a higher BMD baseline, from which declines then occur. Pre- and post SCI BMIs and BMDs are correlated.

Age and Duration of Injury

Aging and bone loss in the post-menopausal population is well documented (Bauer et al. 1993, Siris et al. 2001). In the post menopausal population age becomes important mostly after 50 years. A 10 year increase in age after 50 years is associated with a 1.4 to 1.8 total increase in the incidence of vertebral fractures (Ross 1994). This obviously will not be the rule in the SCI population wherein DOI and age are increasing and so is spine BMD. Anatomical site of study will influence data, e.g. as DOI increases, so does spine BMD but not knee BMD. Age negatively influences BMD of the hip and knee. DOI positively influences the spine and negatively influences the knee; but its effect on the hip is unclear (Garland et al. 2001a, Garland et al. 2001b, Garland et al. 2004b, Garland et al. 2005b). Age and DOI are increasing in parallel; Z-scores, which are normalized for age, sex and race, are available for the spine and hip and provide further insight on the effect of DOI relative to normal aging expectations at those sites. The SCI spine BMD increases with DOI relative to normal aging. The hip appears to demonstrate long-term BMD rebound as well.

Alcohol and Cigarettes

Alcohol and smoking are associated with a decrease in BMD in the able-bodied adult. Alcohol and smoking were not noted to decrease BMD in individuals with SCI (Garland et al. 2004b). Another study, however noted veterans with SCI and hospitalized for fractures had greater alcohol use (Morse et al. 2008). Alcohol herein could be associated with risk taking rather than decreased BMD.

FRAX®

The World Health Organization (WHO) recently developed FRAX® - Fracture Assessment Tool. This web-based tool predicts the ten –year risk of osteoporosis fracture in men and women. Able-bodied individual risk factors (age, weight, etc.) as well as clinical risk factors (prior fragility fracture, smoking, etc.) are entered into the web-based

tool. The FRAX® algorithm then provides a figure indicating a ten-year fracture probability as a percentage, which provides guidance for treatment.

Current knowledge of SCI bone loss precludes the development of an SCI FRAX®. The following factors increase the probability of fractures at the knee in individuals with SCI. Knee BMD is decreased in: completeness (especially tetraplegia), sex (women), low BMI (<25 kg/m^2) age, age at injury (under 18 years), and DOI. Risks for fracture: BMD. <.78g/m^2, complete paraplegia (greater exposure) sex (women), DOI, age, prior fracture, and alcohol.

Fractures and Fracture Threshold

Fracture Threshold

A densitometric diagnosis of osteoporosis is made according to the criteria of the WHO when DEXA measured T-Score (the standard deviation difference between the patient's BMD and that of the young reference population) is -2.5 or lower at the hip or posteroanterior lumbar spine. The WHO classification should not be used for women or men aged 50 years and younger because BMD and fracture risk is not well established in these groups. Certainly, it is not established in the young SCI population or the distal LE sites excluding the os calcis.

The risk of fracture increases as the amount of trauma increases or the ability of the bone to withstand injury decreases, or both. The breaking strength of bone is linearly related to its bone mineral content (BMC), and its measurement at fracture sites determines fracture risk (Riggs et al. 1981). The BMD at a specific site below which most fractures occur has been termed "fracture threshold." A further refinement of this concept established BMD fracture thresholds, a point wherein fractures begin occurring, and BMD fracture breakpoints at values when the majority of fractures occur (Mazess 1990).

A majority of postmenopausal fractures in the general population occur at the spine and hip (femoral neck and intertrochanteric region of the femur). Their assigned fracture threshold values were established at 0.97g/cm^2, 0.95 g/cm^2, and 0.92g/cm^2 respectively (Z scores of -2.3, -2.4, and -2.2 respectively)(Riggs et al. 1981).

Comparison of data from 168 participants between a non-fracture group and a fracture group established fracture thresholds and breakpoints for the SCI knee (Figures 6A & B). The knee fracture threshold was 0.78g/cm2 (-36% loss) with a breakpoint of .49g/cm2 (-57% loss) (Garland et al. 1993, Garland et al. 2005b). These values are similar to another study using a different methodology (Eser et al. 2005). Fracture of the LE begin to occur when the knee BMD (as a proxy for all LE fractures) is 0.86 gm/cm2 (-25% loss). The peak occurrence of LE fractures occurs when knee BMD is at .49gm/cm2 (-57% loss).

Fractures

Fracture studies have mostly been hospital based. This has given a bias towards fractures in the vicinity of the knee progressing proximally (Comarr 1962). Seventy-three consecutive individuals with complete injuries and 100 with fractures presenting to a

community SCI outpatient clinic were evaluated for fracture locations (Garland and Adkins 2001) (Figure 7). Fractures occurred frequently at the knee with some occurring above the knee, but more occurred at the proximal and distal tibia and ankle. The more distal fracture sites have been previously noted and are more consistent with bone loss data (Ragnarsson and Sell 1981; Vestergaard et al. 1998).

The Knee

BMD at the knee may be a good study site for treat outcomes since a significant number of fractures occur herein. The knee is very sensitive to risk factors such as sex, completeness, DOI and age (Garland and Adkins 2001) (Fig 8).

Precise measurement for knee BMD is not readily available. Knee BMD in men with complete paraplegia can, however, be estimated. A person 20 years after injury would have a (–) 46% decrease in knee BMD. This is calculated by adding the sums of acute, sub-acute and chronic BMD decreases: (4 months at (-) 1% loss weekly = (-) 16; (-) 1% loss monthly x 12 = (-) 12; (-) 1% loss annually x 18 = (-) 18%. This individual's knee BMD is below fracture threshold and near fracture break point. Men with complete tetraplegia and women with complete SCI of similar DOI lose more bone placing their BMD near fracture break point. This formula plus knowledge of risk factors may assist in treatment decisions.

Clinical Significance of LE BMD

The greatest BMD decreases occur in the distal LE. This is confirmed clinically by the number of distal fractures (Ragnarsson and Sell 1981, Vestergaard et al. 1998, Garland and Adkin 2001). Fractures in the lumbar spine should rarely occur in this population since BMD is increased herein. The hip will reach fracture threshold and remain in that vicinity with some individuals sustaining fractures. Sufficient exposure such as a fall during transfer may cause the hip to fracture. The knee in individuals with complete injuries, especially women, will reach fracture threshold within 3 years of injury. Fractures begin to occur thereafter (Chow et al. 1996). More fractures are likely to occur in women with complete injuries because they lose more bone (Ragnarsson and Sell 1981, Vestergaard et al. 1998, Garland et al. 2001b). Individuals with incomplete injuries rarely reach fracture threshold and will sustain fewer fractures (Ragnarsson and Sell 1981, Garland et al. 1994). Significant numbers of fractures occur at the knee and distally.

Treatment

Anti-resorptive drugs have potential to modify all three phases of SCI bone loss as well as varying endpoints. Bone markers are tertiary endpoints to treatment and can measure general effectiveness of anti-resorptive treatment during the acute phase of bone loss. Anti-resorptive drugs have been noted to reduce values of bone resorption markers in acute SCI (Craven et al. 2008). BMD is a secondary endpoint and its values may measure effectiveness of anti-resorptive treatment acutely and sub-acutely at specific sites (Craven et al. 2008). Chronically monitoring BMD values may have limited value at the lumbar spine and hip since BMD may increase with DOI. The knee and/or the tibia

may be the best study sites for BMD changes acutely, sub-acutely and perhaps chronically. This requires further analysis.

Fracture reduction is the primary endpoint of treatment (chronic phase). Positive increments of 5-10% occur in the hips and spine in treated able-bodied patients (Sorensen et al, 2003). This percentage increase may not push SCI knee BMD above fracture threshold. However, anti-resorptive drugs only effect small increases in BMD in the lumbar spine and the hip in the able-bodied, but decrease fracture rates by up to 50% at these sites. Although no studies are available to evaluate their effectiveness at SCI fracture reduction, it is theoretically possible that they may eventually be proven effective.

Presently preventive measures are the most effective. Emphasis must be placed on atraumatic transfers, atraumatic rigorous range of motion, even in therapy, especially in the chronic phase, and fall avoidance. Unexplained limb swelling especially after falls must be radiographically evaluated.

Figures

Figure 1

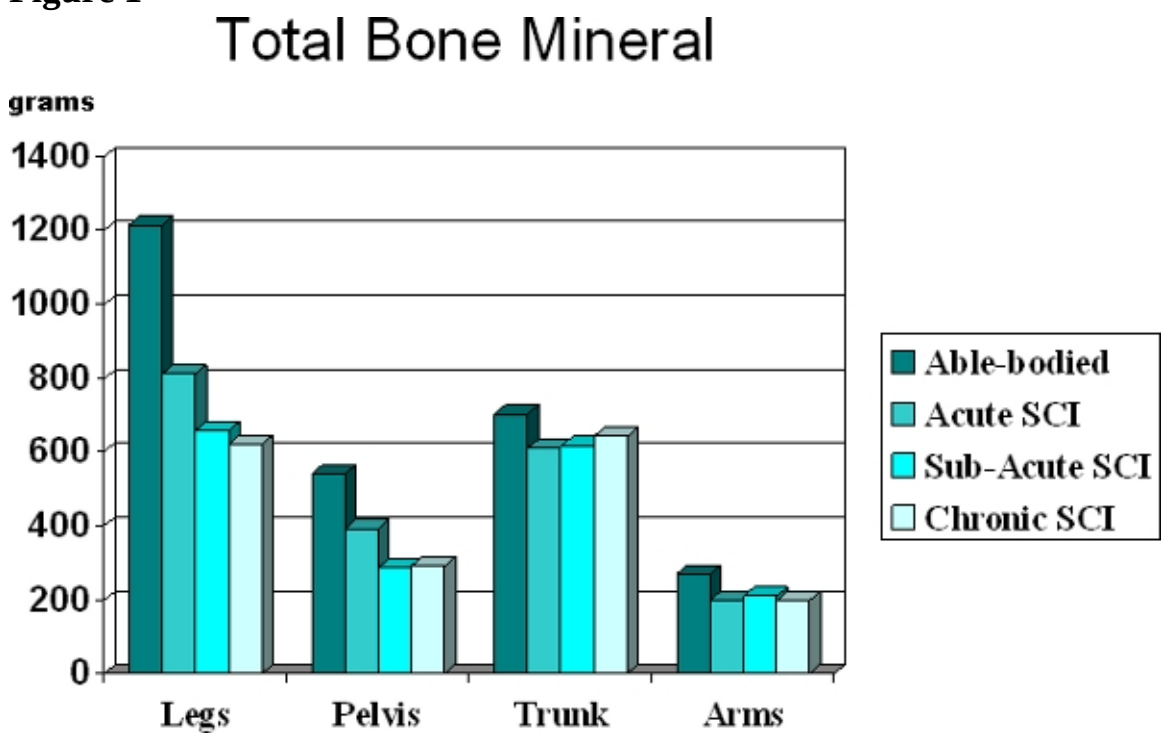


Figure 2

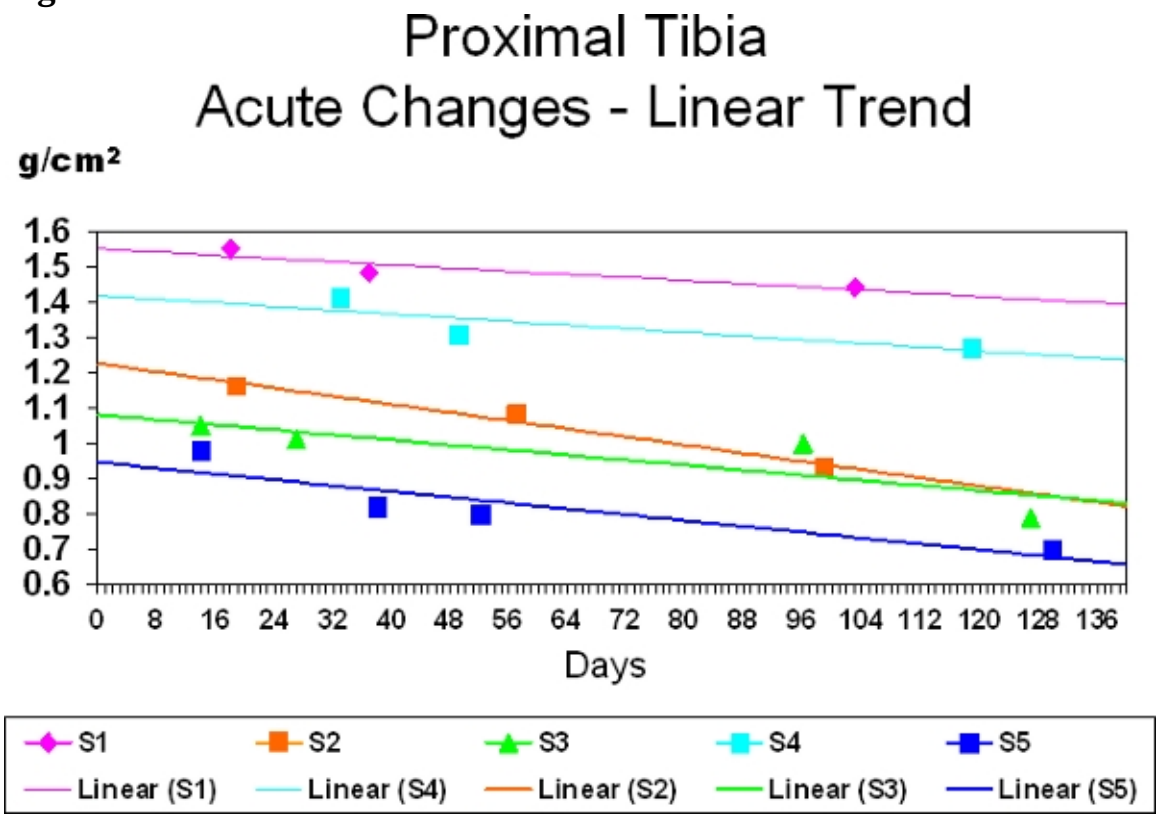

Proximal Tibia
Acute Changes - Linear Trend
g/cm²
1.6
1.5
1.4
1.3
1.2
1.1
1
0.9
0.8
0.7
0.6
0 8 16 24 32 40 48 56 64 72 80 88 96 104 112 120 128 136
Days
S1
S2
S3
S4
S5
Linear (S1)
Linear (S4)
Linear (S2)
Linear (S3)
Linear (S5)

Figure 3

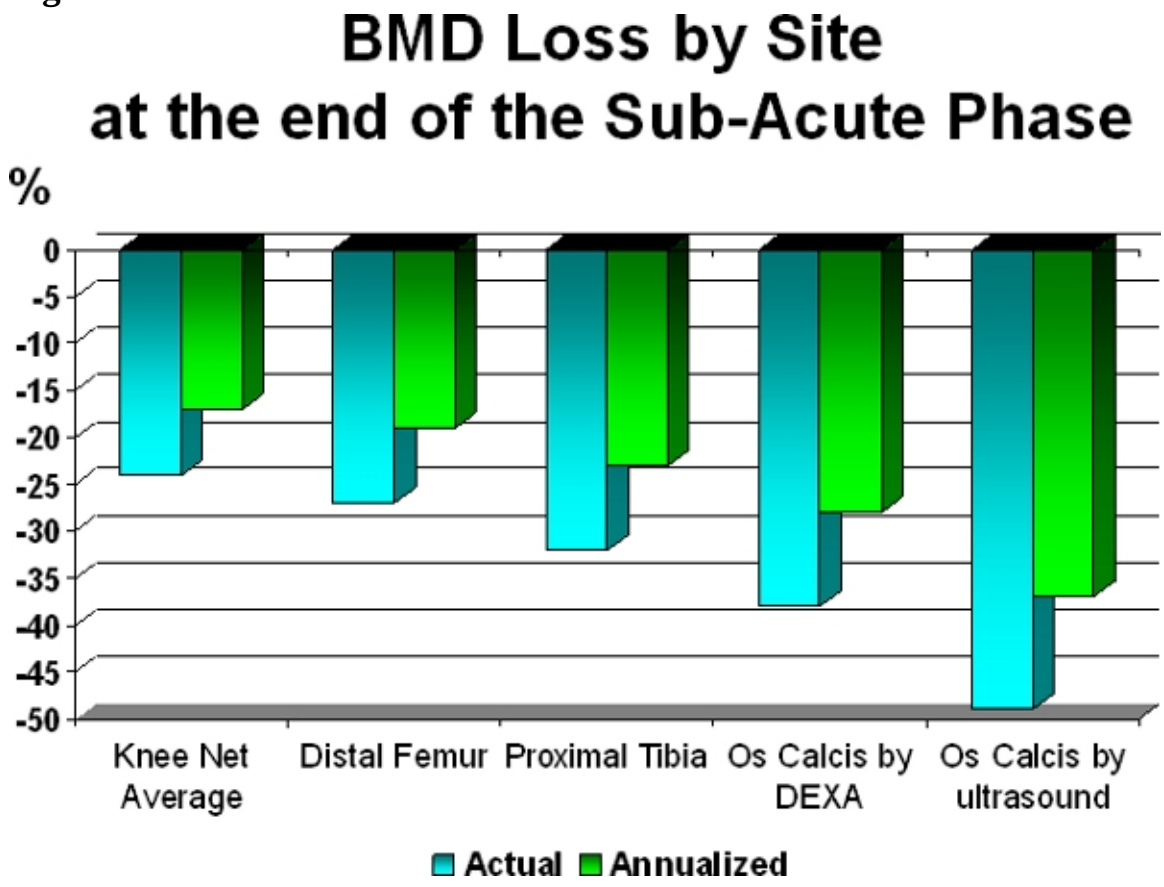

BMD Loss by Site
at the end of the Sub-Acute Phase
%
0
-5
-10
-15
-20
-25
-30
-35
-40
-45
-50
Knee Net Average
Distal Femur
Proximal Tibia
Os Calcis by DEXA
Os Calcis by ultrasound
Actual
Annualized

Figure 4

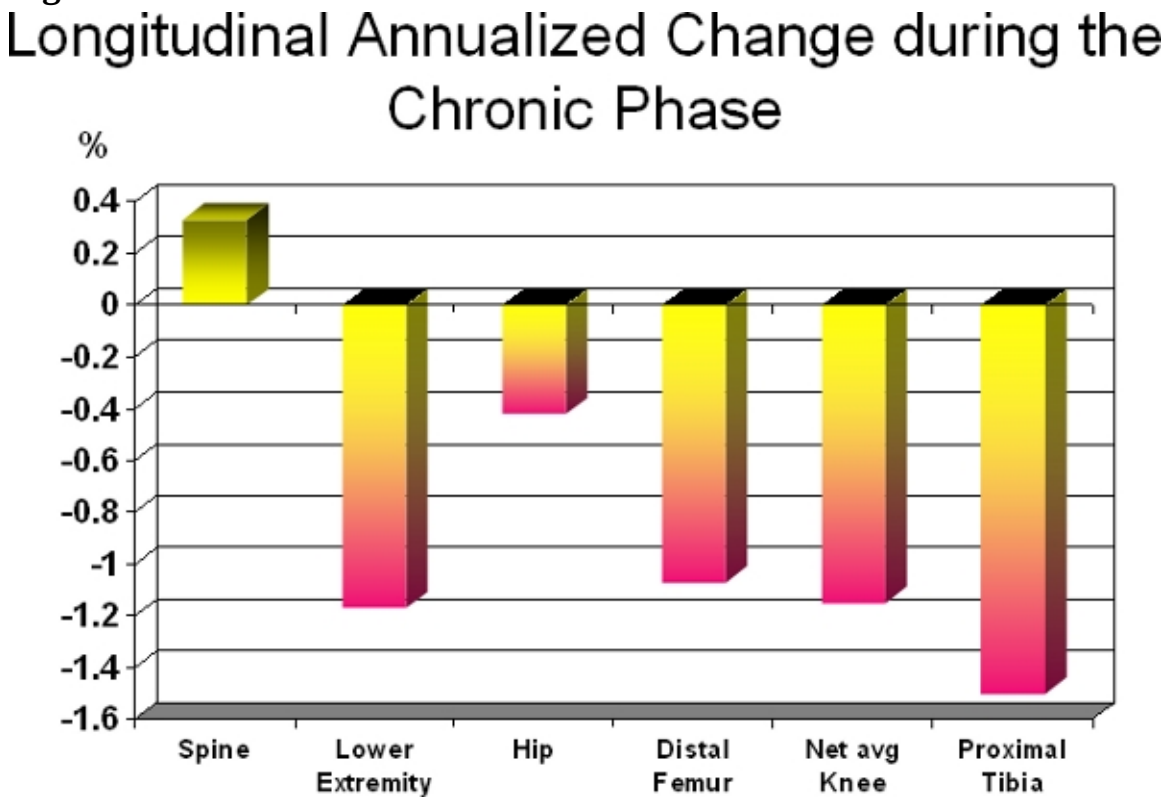
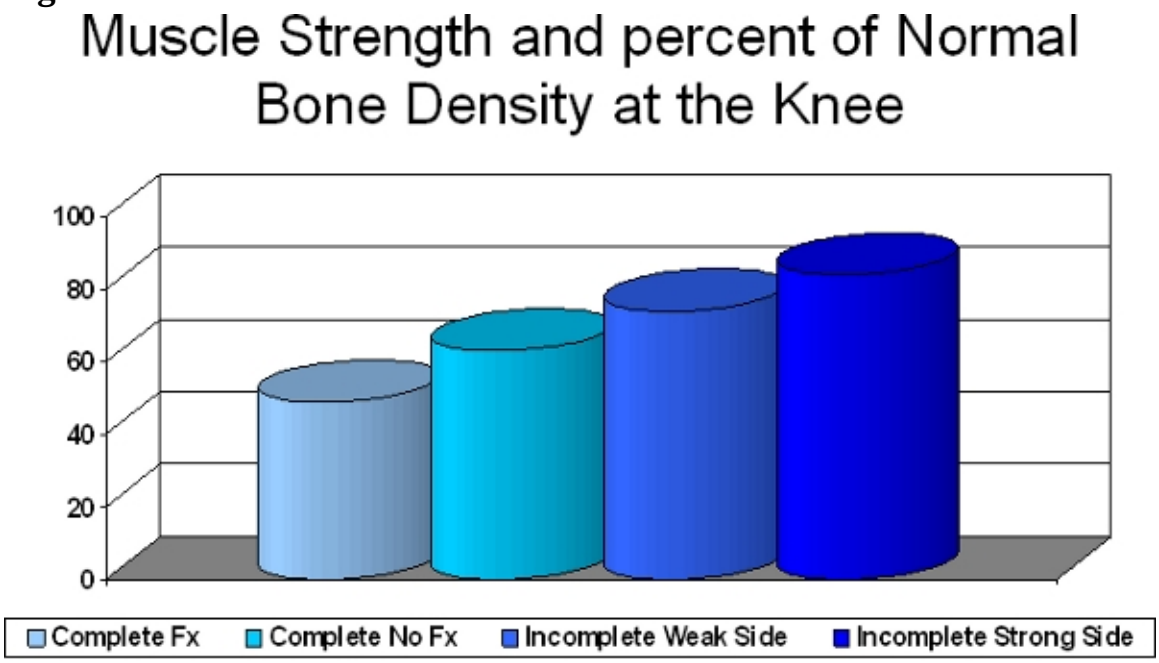

Longitudinal Annualized Change during the Chronic Phase
%
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
-1
-1.2
-1.4
-1.6
Spine
Lower Extremity
Hip
Distal Femur
Net avg Knee
Proximal Tibia

Figure 5



Those with complete loss of muscle voluntary muscle strength with and without fractures (Fx) compared to those with incomplete Brown-Sequard muscle patterns where one side is weak and the other is strong.

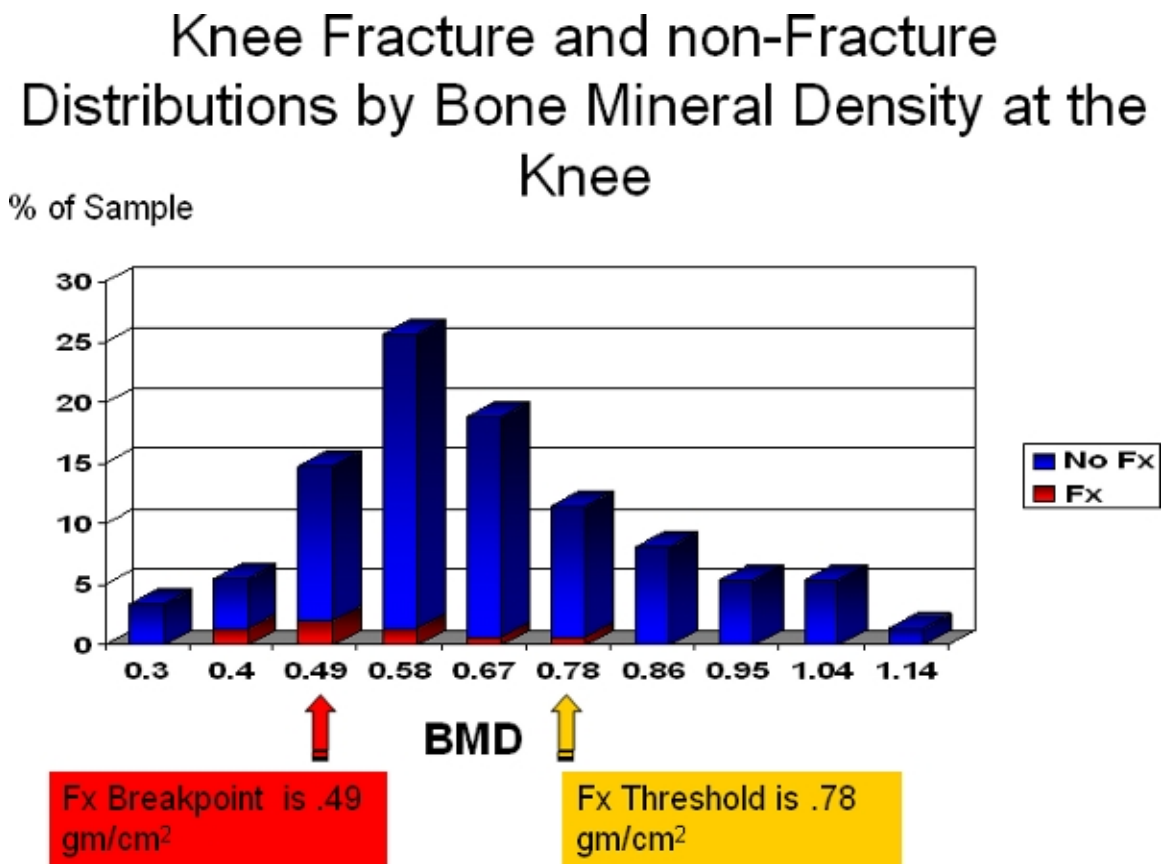

Knee Fracture and non-Fracture Distributions by Bone Mineral Density at the Knee
% of Sample
30
25
20
15
10
5
0
0.3
0.4
0.49
0.58
0.67
0.78
0.86
0.95
1.04
1.14
BMD
No Fx
Fx
Fx Breakpoint is .49 gm/cm2
Fx Threshold is .78 gm/cm2

Figure 6B

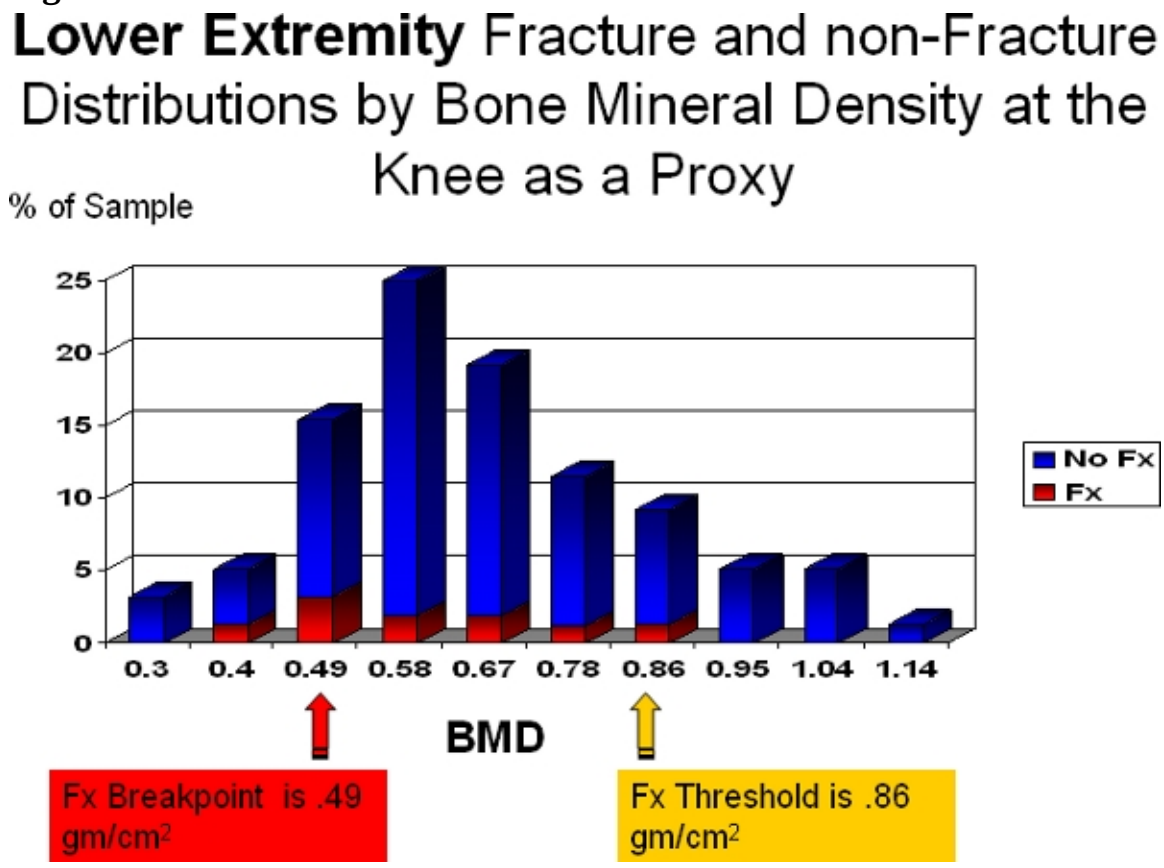

Lower Extremity Fracture and non-Fracture Distributions by Bone Mineral Density at the Knee as a Proxy
% of Sample
25
20
15
10
5
0
0.3
0.4
0.49
0.58
0.67
0.78
0.86
0.95
1.04
1.14
BMD
No Fx
Fx
Fx Breakpoint is .49 gm/cm2
Fx Threshold is .86 gm/cm2

Figure 7

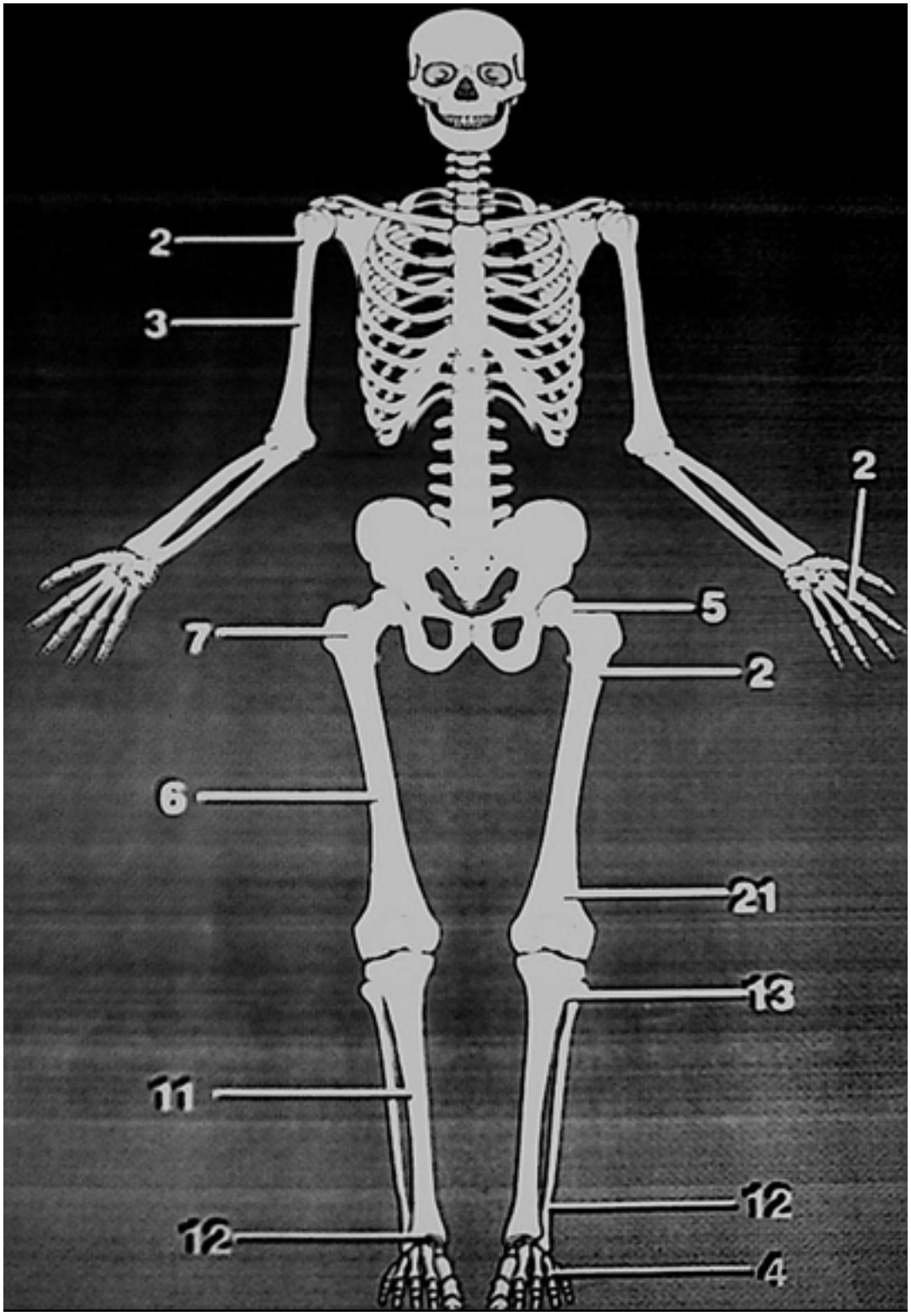
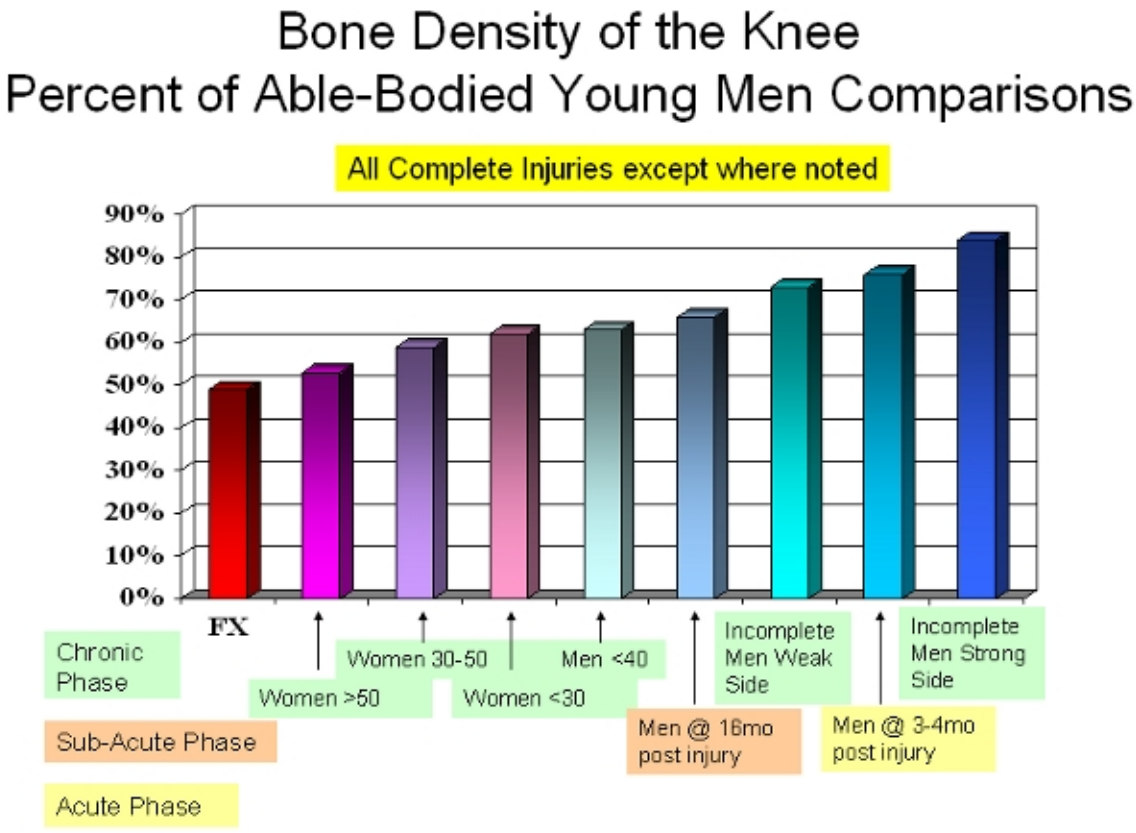


Figure 8



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