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Are uniform regional safety factors an objective of adaptive modeling/remodeling in cortical bone?

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Summary

It has been hypothesized that a major objective of morphological adaptation in limb-bone diaphyses is the achievement of uniform regional safety factors between discrete cortical locations (e.g. between cranial and caudal cortices at mid-diaphysis). This hypothesis has been tested, and appears to be supported in the diaphyses of ovine and equine radii. The present study more rigorously examined this question using the equine third metacarpal (MC3), which has had functionally generated intracortical strains estimated by a sophisticated finite element model. Mechanical properties of multiple mid-diaphyseal specimens were evaluated in both tension and compression, allowing for testing of habitually tensed or compressed regions in their respective habitual loading mode ('strain-mode-specific' loading). Elastic modulus, and yield and ultimate strength and strain, were correlated with *in vivo* strain data from a previously published finite element model. Mechanical tests revealed minor variations in elastic modulus, and yield and ultimate strength in both tension and compression loading, while physiological strains varied significantly between the cortices. Contrary to the hypothesis of uniform safety factors, the MC3 has a broad range of tension (caudo-medial, 4.0; cranio-lateral, 37.7) and compression (caudo-medial, 5.7; cranio-lateral, 68.9) safety factors.

Key words: horse, safety factor; bone adaptation; cortical bone; equine third metacarpal; bone remodeling.

Introduction

Mechanical strains produced by functional loading influence the cellular activities responsible for normal appendicular bone development and maintenance. Contemporary investigations recognize that modeling and remodeling processes mediate the strain-related structural and material adaptations produced during normal bone development. However, the goals towards which such adaptations are directed remain unclear.

Lanyon et al. (1979) hypothesized that a possible objective for regional variations in material organization between cortical locations of a limb bone diaphysis may be the maintenance of uniform stresses throughout a bone's cross-section. Examining mature ovine radii at mid-diaphysis, they found that the narrower caudal 'compression' cortex had a lower elastic modulus than the thicker, less-highly strained cranial (dorsal) 'tension' cortex. Riggs et al. (1993) reported similar elastic modulus differences between the cranial 'tension' and caudal 'compression' cortices of the equine radius at mid-diaphysis, even though these regions have nearly equivalent cortical thickness. These elastic modulus differences were attributed to significant regional variations between the cranial and caudal cortices, including more oblique-to-transverse collagen fiber orientation, lower mineral content, and increased remodeling with secondary osteons in the caudal cortex. These authors suggested that since cranial *versus* caudal stresses are significantly different in each species, and the associated remodeling responses appeared to amplify this difference, the non-uniform stress distribution represents a goal of developmental adaptation. Because yield and ultimate stress of cortical bone are lower in tension than in compression (Reilly and Burstein, 1975), and the non-uniform stress distributions of ovine and equine radii resulted in roughly equivalent safety factors between the cranial and caudal cortices, the achievement of equivalent or uniform 'regional' safety factors (e.g. cranial cortex = caudal cortex) was offered as an explanation for a major goal of adaptation in these bones (Lanyon et al., 1979; Riggs et al., 1993).

Safety factors, when considered in skeletal biomechanics, usually refer to an entire bone (Rubin and Lanyon, 1982; Biewener, 1993). In the present study we further examine the idea of 'regional' safety factors; for example, those from a distinct cortical location within the same transverse cross-section (Lanyon et al., 1979; Riggs et al., 1993). In either case, 'safety factor' refers to the ratio of yield stress (or strain) to peak physiological stress (or strain), and represents a means of quantifying how strong the bone is in relation to how strong it needs to be to avoid fracture (safety factor = yield or ultimate stress / peak physiological stress).

If adaptive remodeling/modeling sufficiently modifies material and/or structural organization to ultimately produce uniform regional safety factors in equine and ovine radii, then other appendicular long bones that experience habitual bending should be similarly adapted. The present study tests this hypothesis in the equine third metacarpal (MC3), which has had functionally generated intracortical strains estimated by a sophisticated finite element model (Gross et al., 1992) (Fig. 1). The habitual strain distribution of the equine MC3 is characterized by habitual bending; the neutral axis passes through the cranio-lateral cortex, the position of which produces a narrow band of tension in this region. The remainder of the cortical cross-section experiences a wide range of compression magnitudes that are maximal in the caudo-medial cortex. The present study followed the methods of Riggs et al. (1993), and applied them to the MC3 as opposed to the radius. Compression and tension testing was performed on machined specimens from cortical locations that characteristically receive *in vivo* tension (cranio-lateral cortex), as well as a range of compression magnitudes (higher in the caudo-medial cortex; lower in the cranio-medial cortex). Analyzing these specimens in the context of their habitual tension or compression strain mode is important for an accurate assessment of their physiological mechanical properties. Regional intracortical safety factors were calculated using the measured mechanical parameters, including elastic modulus, yield and ultimate stress, yield and ultimate strain, and *in vivo* strain data obtained from the finite element model of Gross et al. (1992).

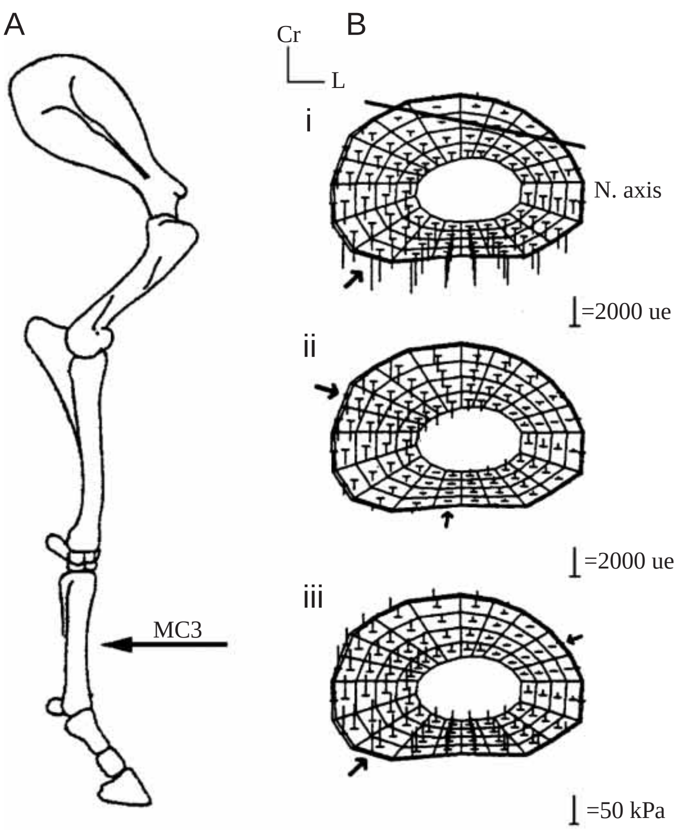

Fig. 1. Finite element model of MC3 (adapted from Gross et al., 1992). (A) The arrow indicates the mid-diaphyseal location of the third metacarpal. (B) Finite element meshes from Gross et al. (1992). Distribution of normal strain (i), shear strain (ii) and strain energy density (iii) acting on the mid-shaft cross-section at the time of peak strain during the gait cycle. Sites of maximum strain are noted by the large arrows, sites of least strain by the small arrows or neutral axis (N-axis). ue=με. [Reproduced from *Journal of Biomechanics* vol. 25, '*Characterizing bone strain distributions* in vivo *using three triple rosette strain gages*,' pp. 1081-1087, Copyright (1992), with kind permission from Elsevier Science.]

Materials and methods

Specimens

Right and left MC3 bones were collected from each of ten skeletally mature horses (Table 1). Bones were obtained in a fresh state from a regional abattoir. The animals had no evidence or history of skeletal pathology, and no animals were involved in racing. Each bone was dissected free of soft tissue. Examination of the interfaces between the splint bones (MC2 and MC4) and the MC3 showed no evidence of fusion. This is important since the experimental animal used in determining the finite element mesh of Gross et al. (1992) (from which the peak strains for determining safety factors were obtained, as described below) also did not have fused splint bones. The bones were wrapped in saline-soaked towels and stored in plastic bags at –20°C.

Mechanical testing

One randomly selected MC3 from each pair was sectioned transversely at 50% of overall length. A 5 mm-thick transverse segment immediately proximal to the mid-diaphyseal transection was used to obtain specimens for compression testing. Using a diamond blade saw and continuous water irrigation, six 5 mm×5 mm×5 mm cubes were cut from each of the ten bones; cortical locations were cranio-lateral (*N*=2; 20 total specimens), lateral (*N*=1; 10 total specimens), caudo-medial (*N*=2; 20 total specimens) and cranio-medial (*N*=1; 10 total specimens) (Fig. 2A). These locations were representative of bone from cortical areas that experience tensile strains, as well as a range of compression magnitudes.

Mechanical testing was conducted on saline-moistened specimens that had equilibrated at room temperature according to methods of Riggs et al. (1993). Although they used 8 mm×8 mm×8 mm cubes in compression testing of equine radii, we used 5 mm×5 mm×5 mm cubes because of narrower cortices in some locations.

From the contralateral bones, a 50 mm-thick segment of cortex was sectioned transversely such that the midpoint was at 50% of bone length. Rectangular slabs cut from this segment were milled to match the size and shape of the dumb-bell shaped specimens used for tension testing by Riggs et al. (1993) as described by Evans et al. (1992) (Fig. 3). Two specimens from the 'tension' (cranio-lateral) cortex and two from the 'compression' (caudo-medial) cortex were milled from each bone (Fig. 2B). Only three tension specimens were milled from two bones with narrow cortices (38 total specimens).

During specimen machining, orientation of the long axes of tension and compression specimens remained parallel to the original longitudinal diaphyseal axis. To avoid untoward effects of freezing on mechanical behavior, all specimens were allowed to equilibrate in a moist state at room temperature for 24 h prior to testing (Evans et al., 1992).

Using an Instron Model 4303 (Canton, MA, USA) with a 25 kN load cell, cubic specimens moistened with saline were compressed to failure along the longitudinal diaphyseal axis

Table 1. *Animal and bone profile*

				Test limb	
Specimen	Breed	Gender	Age (years)	Tension	Compression
1	Data unavailable	Female	7	Right	Left
2	Data unavailable	Female	14	Right	Left
3	Quarter horse	Female	3	Right	Left
4	Quarter horse	Female	18	Left	Right
5	Quarter horse	Female	17	Left	Right
6	Paint	Male	8~12	Left	Right
7	Quarter horse	Female	2	Left	Right
8	Paint	Female	2	Left	Right
9	Quarter horse	Gelding	11	Right	Left
10	Quarter horse	Female	4	Right	Left

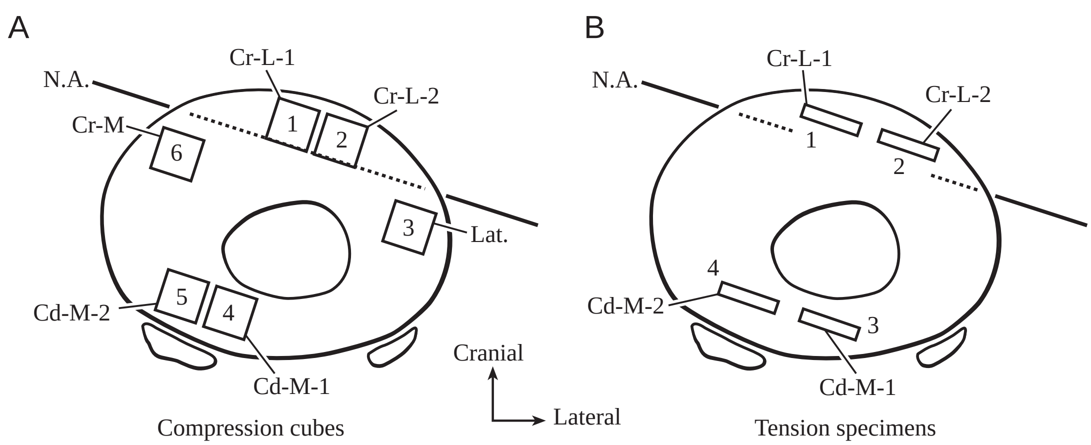

Fig. 2. Compression and tension specimen locations in the MC3. (A) Locations of the six compression 'cube' specimens: cranio-lateral (2), lateral (1), caudo-medial (2), and cranio-medial (1). (B) Locations of the four tension 'dumb-bell' specimens: cranio-lateral (2), caudo-medial (2). N.A., neutral axis.

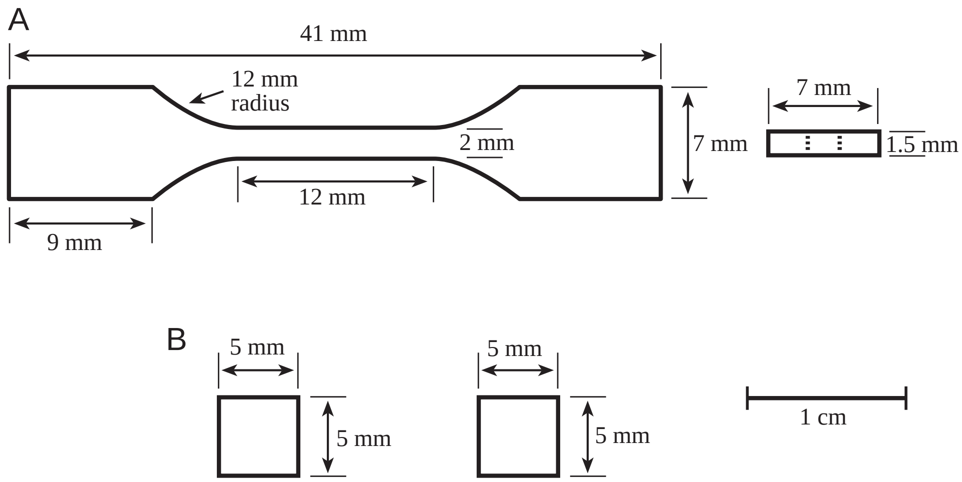

Fig. 3. Specimen geometry. (A) Tension (dumb-bell-shaped) and (B) compression. (A reproduced with revision from *Equine Veterinary Journal* vol. 24, '*The response of equine cortical bone to loading at strain rates experienced in vivo by the galloping horse*,' pp. 125-128, with kind permission from *Equine Veterinary Journal*.)

unrestrained between parallel platens at a strain-controlled rate of 0.001 s^{-1}. Certified material standards were used to calibrate the load cell and validate the accuracy of the crosshead displacement. Strain measurements were obtained from the measured crosshead displacement, and were corrected for machine compliance (determined by loading the machine against itself).

Tensile tests were performed using an MTS 858 Bionix (Eden Prairie, MN, USA) testing machine with a 20 kN load cell interfaced with a ±2 kN load cartridge. Tensile specimens were held by identical grips that spanned the transverse breadth of the specimen ends. This allowed elongation along the anatomical longitudinal axis. Specimens, moistened with saline, were loaded to failure at a strain-controlled rate of 0.01 s^{-1}. (The use of different strain rates in compression and tension is in accordance with Riggs et al., 1993; C. M. Riggs, personal communication.) Strain measurements were obtained using an MTS 632.13F-20 extensometer (Eden Prairie) attached to each specimen with rubber O-ring fasteners.

Elastic modulus, yield stress and strain, and ultimate stress and strain were determined for each specimen in both tension and compression testing, with yield point defined at 0.2% strain offset. Although this strain–offset yield criterion is arbitrary, it is commonly used to define material yield (ASTM: Standard Test Method for Young's Modulus, Tangent Modulus, and Chord Modulus, Designation E111-82. In *1992 Annual Book of ASTM Standards*, Edited, pp. 288-293; Philadelphia, ASTM).

Mechanical data from specimens were excluded if they: (1) failed catastrophically (i.e. at low stress) early in testing, or (2) fractured outside the location between the two extensometer clips.

Regional safety factors

Normal physiological strain values used in calculating regional safety factors were obtained from the finite elemental mesh of Gross et al. (1992) (Fig. 1). The value used for each location was the mean of values from three adjacent mesh cells that most closely corresponded to the locations from which specimens used in mechanical testing were obtained. In accordance with the stress–strain relation of Hooke's Law (σ=Eε; Gere and Timoshenko, 1984), physiological stress (σ) data were calculated using the elastic modulus (E) in tension and compression (experimentally determined in the present study) and the published strain (ε) values (Gross et al., 1992). Yield safety factors were calculated as the ratios of yield stress to peak physiological stress, and ultimate safety factors as the ratio of ultimate stress to peak physiological stress.

Strain values reported by Gross et al. (1992) were obtained from the MC3 of a 460 kg, 5-year-old Thoroughbred that had not been race training for at least 1 year prior to experimentation. The strain distributions published in their studies of Thoroughbreds at sub-maximal speeds are 'virtually identical' to those that have been measured using the same methods at the mid-diaphyses of quarter horses during similar gaits (T. S. Gross and C. T. Rubin, personal communication).

Statistical analysis

A one-way analysis of variance (ANOVA) design with Fisher's PLSD test for evaluating multiple-paired comparisons was used to assess regional variations for each of the mechanical parameters.

Results

Mechanical testing

The general mechanical properties found are shown in Table 2. There were no statistically significant differences in elastic modulus in tension-tested specimens (P>0.5). In compression tests, the cranio-medial location had a significantly higher stiffness than the cranio-lateral location (P<0.05).

In general, averaged elastic modulus values were on the order of 30% higher in tension testing of bone habitually loaded in tension (17.81 GPa) when compared to compression

Table 2. *Summary of mechanical properties in cortical locations of equine third metacarpals*

Test mode	Cortical region	*N*	Elastic modulus (GPa)	Yield stress (MPa)	Yield strain (%)	Ultimate stress (MPa)	Ultimate strain (%)	Physiological stress (MPa)	Yield safety factor	Ultimate safety factor
Tension	Cranio-lateral (T)	12	17.81±1.86	148.59±15.45	1.00±0.07	161.20±17.73	3.38±0.79	3.95±0.32	37.72±3.49	40.93±4.18
	Caudo-medial (C)	17	17.26±2.21	148.07±17.36	1.02±0.15	163.85±17.02	3.73±0.84	37.13±4.84	4.04±0.62	4.46±0.59
Compression	Cranio-lateral (T)	20	11.88±3.04	172.04±20.79	1.76±0.50	182.87±16.54	2.89±2.50	2.65±0.67	68.89±20.09	73.86±23.35
	Caudo-medial (C)	20	12.98±2.56	157.71±23.25	1.45±0.15	170.28±15.13	2.11±0.49	28.00±5.39	5.71±0.70	6.23±0.89
	Lateral (C) (C,T?)*	10	13.92±4.56	158.57±40.01	1.39±0.20	174.38±17.89	1.93±0.86	11.36±3.72	14.39±2.61	17.39±8.22
	Cranio-medial (C)	10	14.30±2.76	185.68±23.85	1.53±0.14	191.54±21.72	2.00±0.57	3.46±0.67	54.45±5.98	56.45±7.91

Values are means ± S.D.; *N*=number of specimens.
T, specimen obtained from a bone region subject to habitually prevalent tensile strains.
C, specimen obtained from a bone region subject to habitually prevalent compressive strains.
*This region may receive predominant tension at higher gait speeds.

testing of bone habitually loaded in compression (13.64 GPa, mean of caudo-medial and cranio-medial) (P<0.01).

In tension tests, yield stress values were nearly equivalent (P>0.5). In compression tests, the cranio-medial location exhibited the highest yield stress values compared to the lateral and caudo-medial cortical locations, which exhibited the lowest (P<0.05). Tension tests of habitually tensed bone revealed lower yield stress (148.59 MPa) compared to compression tests of habitually compressed bone (171.70 MPa, mean of caudo-medial and cranio-medial) (P=0.30 for caudo-medial *versus* cranio-lateral; P<0.001 for cranio-medial *versus* cranio-lateral).

In tension tests, ultimate stress values were not significantly different (P>0.5). In compression tests, ultimate stress data showed moderate regional variations (P<0.03 for caudo-medial *versus* cranio-lateral; P<0.01 for caudo-medial *versus* cranio-medial).

During tensile testing, premature catastrophic failure (failure at low stress) and/or failure outside the region between the extensometer clips resulted in seven specimen exclusions from the cranio-lateral region, and two exclusions from the caudo-medial region. No failures occurred at the gripped ends. Three compression specimens from the lateral cortex were also excluded for premature catastrophic failure (failure at low stress).

Safety factors

Calculated yield and ultimate safety factors (Table 2 and Fig. 4) show large regional variations in both tension and compression modes of loading. The cranio-lateral ‘tension’ cortex has a tension safety factor of 37.7 while the caudo-medial ‘compression’ cortex has a compression safety factor of 5.7 (P<0.0001) (Fig. 5).

Discussion

Contrary to the idea that uniform regional safety factors may be a goal of adaptive modeling/remodeling (Lanyon et al., 1979; Riggs et al., 1993), large regional variations were observed across the mid-diaphyseal equine MC3. Since yield and ultimate stress of cortical bone are lower in tension than in compression (Reilly and Burstein, 1975), uniform stress distributions should result in lower safety factors in a habitually tensed cortex compared to a habitually compressed

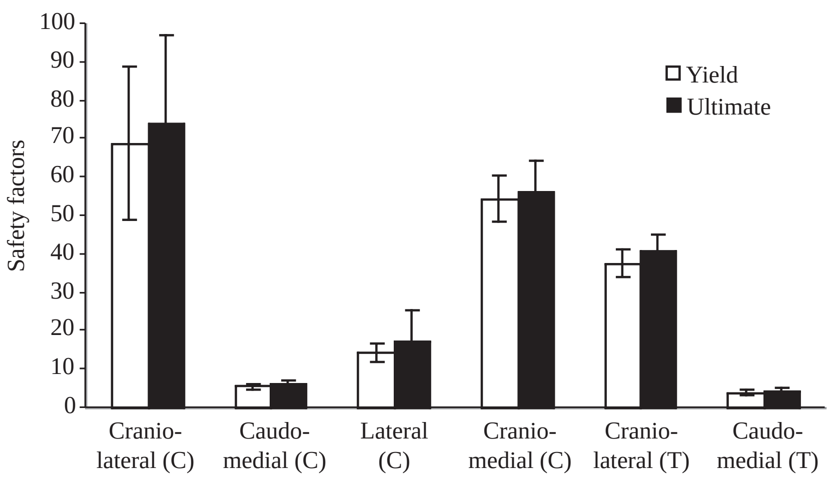

Fig. 4. Regional (intracortical) safety factors in the equine MC3, showing both yield and ultimate safety factors for each cortical region and testing mode. C, compression-tested; T, tension-tested. Values are means ± S.D.

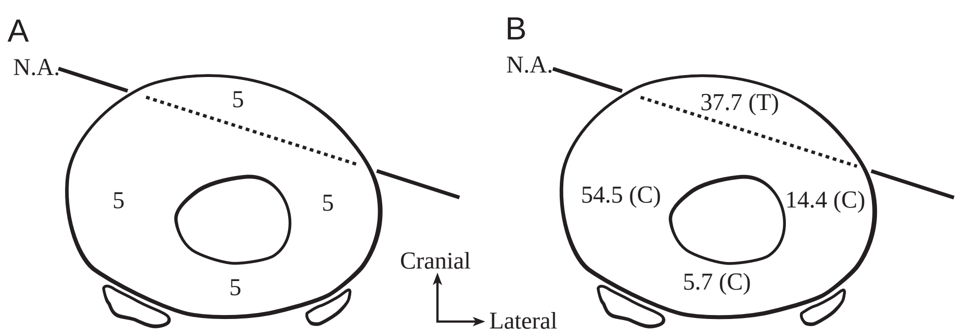

Fig. 5. Comparison of uniform-safety-factor hypothesis *versus* actual findings in the equine MC3. (A) Cross-section of the MC3 showing equivalent safety factors as proposed by the uniform-safety-factor hypothesis. (B) Cross-section of the MC3 based on present data showing large variations in regional yield safety factors. Values shown are based on ‘strain-mode-specific’ testing [i.e. tension testing (T) of the habitually tensed cranio-lateral cortex and compression testing (C) of the habitually compressed caudo-medial cortex]. N.A., neutral axis.

cortex. However, stress distributions are typically non-uniform in limb bone diaphyses because physiological loading has axial and eccentric components that shift the neutral axis away from, and thus amplify stresses in, the compression cortex. Consequently, uniform regional safety factors are possible only if regional differences in material properties are sufficient to cause elastic moduli to have a strong negative relationship with stress or strain. Equine MC3s would therefore need to exhibit large regional variations in elastic moduli and yield stresses between the sampled locations. In contrast, little intracortical variation was shown in these mechanical properties between the cranio-lateral and caudo-medial cortices in both compression and tension loading. Although relatively minor in this context, the regional material variations that do occur, as reported in recent studies, may represent adaptations for other mechanical functions, including energy absorption (Skedros et al., 2000, 2001a, 2003a).

Although the strain distribution obtained by Gross et al. (1992) is highly consistent in quarter horses and Thoroughbreds (T. S. Gross and C. T. Rubin, personal communication), there are a number of limitations in using the strain values obtained from this finite element model. For example, the strain data of Gross et al. (1992) were obtained from one mature horse, and homogenous material properties were assumed. C. Les (personal communication) suggested to us that the use of homogeneous (*versus* heterogeneous) material properties in this model would underestimate cranial and caudal stresses, and overestimate medial and lateral stresses. Additionally, age-related splint-bone fusions may affect the strain distribution of the MC3 (Les et al., 1995). For example, uniform splint bone fusion could shift the habitual neutral axis toward the medullary canal. This would increase safety factors in the caudo-medial cortex and decrease safety factors in the cranio-lateral cortex. However, when considering the limitations of applying the finite element model and the most exaggerated influences that these additional variables might have on a habitual strain distribution, it is clear that the nearly sixfold difference in safety factors on opposing sides of the neutral axis would, at most, be reduced to a threefold difference. This estimate was largely based on a shift in the neutral axis and the recalculation of regional safety factors using the highest strains on the cranio-lateral ‘tension’ periosteal cortical surface, and the lower strains near the endosteal surface of the caudo-medial ‘compression’ region (Fig. 1).

Our calculation of safety factors involves a number of assumptions, and may be problematic since the only values that were considered were normal stresses. Since the normal stresses, and therefore normal strains, fall to effectively zero at the neutral axis, bone along this axis will have, essentially, an infinite safety factor. The presence of other strain characteristics and their distributions, such as shear and strain energy density, were estimated by Gross et al. (1992) but not considered in our calculations. Such alternative strain and/or strain-related stimuli may influence the local cellular environment and the modeling/remodeling processes that mediate the attainment of regional or overall safety factors. Furthermore, Biewener et al. (1983a,b) clearly showed that during acceleration, deceleration and jumping, the distribution of strains and peak stresses change significantly in the equine MC3. Although Gross et al. (1992) made measurements across a range of gait speeds, averaging of cycles may underestimate peak MC3 stresses resulting from acceleration and deceleration. Nunamaker (2001) has also shown that strain in the equine MC3 is significantly dependent upon gait speed, the dorsal surface shifting from predominant tension to predominant compression at higher speeds. This challenges our assumptions about a ‘habitual’ loading state in this bone, implying that our sole focus on the finite element data of Gross et al. (1992) greatly oversimplifies the loading environment that may influence regional safety factors and other possible adaptive changes.

The model of Gross et al. (1992), however, provides a reasonable estimation of peak strains encountered during common, unremarkable ambulation as this model represented a medium-speed trot, which the animal tended toward in pasture. The hypothesis that uniform regional safety factors represent a major goal of a bone’s morphological adaptation reflects the often-suggested idea that peak stresses or strains produced during vigorous activities strongly influence bone adaptation (Currey, 1984; Martin and Burr, 1989; Biewener, 1993; Nunamaker, 2001). Recent literature suggests that adaptive modeling may be sensitive to relatively few highly intensive loading events (Biewener and Bertram, 1994; Skerry and Lanyon, 1995). Alternatively, there are experimental data suggesting that a bone modeling-mediated organization is governed by aspects of the strain environment that may not be linked to the relatively high strains associated with peak and/or yield stresses (Rubin et al., 1990; Rubin and McLeod, 1996; Fritton et al., 2000). These views, although disparate, both suggest that bone modeling is stimulated preferentially by a small subset of its total strain experience. It is also unclear if a relationship exists between the strains that influence bone modeling/remodeling objectives and the strains that are potentially associated with structural failure. These issues clearly pose a significant problem when judging localized regional safety factors or their adaptive relevance from a single load/strain distribution as was done in the present study.

Adaptive morphological variations may be more strongly influenced by strains produced by habitual physiological bending, rather than less-frequent peak or yield strains as suggested by the uniform-safety-factor hypothesis. Experimental studies have demonstrated that limb bone diaphyses of terrestrial animals typically receive spatially and temporally consistent strain distributions during controlled, gait-related activities (Lanyon et al., 1979; Biewener et al., 1986; Biewener, 1993; Fritton and Rubin, 2001). In nearly all limb bone diaphyses that have been studied, the percentage of total normal strain due to bending (hence tension and compression strains) exceeds 70% of the longitudinal strains experienced by a diaphyseal region (Rubin, 1984; Fritton and Rubin, 2001). Additionally, peak *in vivo* tensile strains on limb bone diaphyses are typically 70–85% as large as peak compressive strains (Biewener and Taylor, 1986; Biewener, 1993). The regional predominance of differing strain modes (e.g. tension *versus* compression) and the corresponding disparity in strain magnitude (greater in the compressed cortex) may evoke regional strain-related adaptive responses. For example, compressed regions tend to have greater osteon population density and/or more oblique-to-transverse collagen fiber orientation than opposing tension cortices (Marotti, 1963; Lanyon and Bourn, 1979; Bouvier and Hylander, 1981; Portigliatti Barbos et al., 1984; Martin and Burr, 1989; Mason et al., 1995; Skedros et al., 1994, 1996, 1997, 2001b; Takano et al., 1999; Kalmey and Lovejoy, 2002).

Prevalent bending of long bones may convey functional advantages. Frost (1983) and Lanyon (1980) have suggested the existence of a minimum strain threshold below which bone tissue homeostasis is disrupted, and increased absorption leads to a negative bone balance. Bone curvature may be a means of ensuring that strains safely exceed this threshold. Lanyon (1980) postulated that improved attenuation and absorption of forces are structural advantages of bending. He also considered the dangers of aberrant loads on a bone designed only to withstand axial loading, and suggested that curvature may be a way in which customary strain values might be brought within a particular range.

An explanation more tenable than the achievement of uniform regional safety factors is that structural/geometric variations in the equine MC3, such as cortical thickness differences and cross-sectional shape asymmetry, are naturally selected for enhancing 'loading predictability' during typical use (Bertram and Biewener, 1988). The existence of a predictable loading regime and its coexisting predictable strain distribution probably convey fundamentally important signals for limb bone tissue/organ growth and maintenance (Bertram and Biewener, 1988; Skedros et al., 1996). If maintaining a predictable strain environment is a goal of a bone's hierarchical morphological organization, then which characteristics are most likely to have been modified to achieve this loading predictability? Bertram and Biewener (1988) have argued that this can be readily achieved by modeling processes, which affect structural characteristics such as bone curvature, cross-sectional shape and cortical thickness. These characteristics primarily affect stiffness and strength of a whole bone. Since the equine MC3 lacks longitudinal curvature, loading predictability in this bone is probably achieved by the asymmetry in cortical thickness, which enhances whole-bone flexure in the cranio-lateral to caudo-medial direction (Les, 1995; C. Les, personal communication). Therefore, material adaptations achieved *via* osteonal remodeling would neither be required nor expected for achieving regional or whole-bone stiffness/strength requirements in the vast majority of cases (Woo et al., 1981; Rubin and Lanyon, 1982; Alexander, 1998; A. A. Biewener, personal communication). In contrast, Riggs et al. (1993) cite regional variations in collagen fiber orientation and the corresponding regional variations in elastic moduli as being important in influencing how the whole mid-diaphyseal equine radius strains under functional loads. This disparity in elastic modulus led Riggs et al. (1993) to support the uniform-safety-factor hypothesis that was tested in this study.

If modeling processes are responsible for increased structural strength and are more effective in controlling strains *via* directional bending, then what purpose do the regional material variations such as osteon population density and collagen fiber orientation produced by remodeling serve? In recent studies examining regional material variations in equine MC3s, regression analyses of histocompositional variations and mechanical properties show strong correlations between regional collagen fiber orientation and energy absorption in 'strain-mode-specific' testing (e.g. compression testing of bone from regions habitually loaded in compression *in vivo*; Skedros et al., 2000, 2001a). While the magnitudes of these variations may not be sufficient to affect how a bone's entire cross-section strains under load (Gross et al., 1992), they might enhance other important mechanical properties including local energy absorption, toughness and fatigue resistance (Skedros et al., 2000, 2001a, 2003a,b).

Although the ultimate effects of bone remodeling may produce 'enhanced' regional material properties, the causal mechanisms that mediate these regional variations are not clear. It is plausible that the varied manifestations of bone remodeling (e.g. differences in collagen fiber orientation, and secondary osteon orientation, population density, cross-sectional area and central canal porosity) may reflect responses to microdamage or strain transduction associated with strain distributions developed by a bone's particular shape. The shape may be advantageous and the remodeling the secondary consequence. Thus the regional variations in material properties may not be primary 'objectives' in a context of biomechanical adaptation. In turn, since safety factors are likely to be only one of several considerations of bone modeling/remodeling, the achievement of adequate safety factors could be a consequence, rather than an objective, of bone modeling/remodeling. Clearly, the causal mechanisms that mediate the modeling/remodeling processes that produce and maintain an 'adapted' bone diaphysis, and the ultimate goals of this adaptation, are not well understood.

It is important to note that in some cases apparently high regional cortical safety factors may not be sufficient to avoid failure. For example, the cranio-lateral cortex has a tension safety factor of 37.7, compared to a compression safety factor of 5.7 in the caudo-medial cortex (Table 2, Fig. 5). However, the majority of stress fractures in the equine MC3 occur in the cranio-lateral cortex (Nunamaker, 2001). Such fractures are more common in Thoroughbreds, which probably reflects their relatively fast racing speeds and lower cross-sectional moments of area. However, in all racing breeds it is not entirely clear why microcracks tend to form more frequently in the cranio-lateral cortex. Nunamaker (2001) has suggested that prevalent tensile strains produced in this region during race training enhance specific adaptations for tension. At higher racing speeds, however, this tension-adapted region receives more prevalent, high magnitude compression strains, which promote microcrack formation. Reilly and Currey (2000) showed that damage formed in compression is highly detrimental to tensile mechanical properties. Microdamage can also occur with different frequency and can exhibit different characteristics (e.g. length and shape) in compression *versus* tension cortices (Reilly et al., 1997; Boyce et al., 1998; Reilly and Currey, 1999; Muir et al., 1999). Also, the prevalence of shear strains, which can be more deleterious than tensile strains, probably increases in the cranio-lateral cortex during racing, since the neutral axis (where longitudinally oriented shear strains are maximal) traverses this region at higher gait speeds (Gross et al., 1992). These possibilities and the mechanical test results reported in recent studies (Skedros et al., 2000, 2001a, 2003a), suggest the importance of other 'types' of safety factors that are strongly dependent on accommodating and/or resisting microcrack formation including fatigue resistance, toughness and/or energy absorption.

The second and fourth metacarpal 'splint' bones (MC2 and MC4) may also have important load sharing functions – supplementing the lower safety factors of the caudal cortex – since they extend to approximately mid-diaphysis. Piotrowski et al. (1983) have shown that splint bones have important influences on inertial properties such as the second moment of area (and hence bending rigidity) in the proximal one-third diaphysis. Near mid-diaphysis, however, splint bones of younger horses (<2 years old) typically are not fused to the MC3 (Les et al., 1995), and therefore have minimal influence on bending rigidity (Piotrowski et al., 1983). Splint-bone fusion, which is more common in animals >2 years (Les et al., 1995), may enhance local loading-carrying capacity (e.g. on the order of 10–15% increased bending rigidity in the cranio-caudal axis) (Piotrowski et al., 1983; Nunamaker, 2001). These facts demonstrate that cortical thickness, which can be enhanced in the caudal cortices by splint-bone fusion, may help resist deleterious loading conditions. This is an important issue since the finite element mesh of Gross et al. (1992) was based on an animal with unfused splint bones near mid-diaphysis. This justified the exclusion of any load-carrying function of the splint bones in their finite element mesh. In all animals used in the present study, the splint bones were also not fused near mid-diaphysis.

In summary, results of the present study challenge the idea that the achievement of uniform regional safety factors is a goal of adaptive modeling/remodeling. Since this study only examined normal strain data, it is plausible that safety factors based on other criteria may yield different conclusions. Characterizing 'habitual strains' can be quite difficult, and it is clear that the distribution of strain in the equine MC3 varies considerably with gait speed, acceleration, deceleration and jumping. The myriad of plausible interpretations and caveats that readily emerge when considering the 'objectives' of bone modeling/remodeling processes, and the current lack of consensus on the role of strain in mediating these processes, emphasize the need for additional studies. In this context, and based on our calculations showing non-uniform, normal-strain-based safety factors, we speculate that regional safety factors will not show uniformity, regardless of how they are defined or calculated. As suggested above and supported by mechanical testing data in recent studies (Skedros et al., 2000, 2001a, 2003a,b), it is likely that the non-uniform strain distribution strongly influences the secondary development of the regional material heterogeneity in order to enhance bone toughness, energy absorption and/or fatigue resistance. Such strain-related heterogeneities might represent the ultimate goal of regional adaptation in the equine MC3 and other long bones that are subject to habitual bending.

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