Reduced Loading of the Femoral Neck with Aging is Correlated with Regional Changes in Collagen Fiber Orientation but not Osteon Morphotypes or Population Densities

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Introduction: Mayhew et al. [1] concluded that femoral neck (FN) fragility increases with age, especially in women, because underloading of the superior cortex leads to atrophic thinning of this region. As a result of this localized cortical thinning, "elastic instability" increases to the extent that it might trigger hip fracture in a sideways fall. Here, increased elastic instability is associated with reduced tissue toughness (the capacity to absorb energy through microscopic damage) to the extent that it becomes unable to contribute to fracture prevention. Mayhew et al. also emphasized that the importance of their study lies in clearly showing how substantial the effect of cortical thinning in the superior cortex and associated loss of elastic stability is in explaining the increasing incidence of FN fractures with age. This is clinically significant because the cortex is much more important than trabecular bone in carrying stresses [2]. Hip fracture cases show some additional reduction of the elasticity of the FN, due in part to increased porosity [3] and to a lesser extent reduced tissue density [4]. These findings suggest that elastic instability might be influenced by regional changes in additional histomorphological (i.e., material) characteristics that might be even more influential in effecting tissue toughness of the FN cortex (e.g., regional changes in collagen cross-linking and predominant collagen fiber orientation) [5]. If this is possible, then this could represent a plausible therapeutic target for reducing age-related hip fragility that is likely different from the stimuli that naturally increase overall FN diameter with age (which is considered the primary means for curbing age-related increased elastic instability) [6,7]. The present study focuses on determining if there are material changes in the FN cortex that might curb elastic instability by adjusting the tissue composition/organization in ways that would be expected to most substantially influence toughness—changes in bone collagen organization. We hypothesized that with aging the superior FN cortex experiences reduced stress that eventually becomes net tension in the elderly (Fig.). We predict that because tension is comparatively more deleterious than compression these changes in load history would evoke strain-mode-related adaptation; namely, increased longitudinal collagen fiber orientation (CFO) in the superior "tension" cortex when compared to oblique-to-transverse CFO in the inferior "compression" cortex.

Methods: 29 human FNs (4 M, 25 F; 18-95 yrs) were embedded in methacrylate and a mid-transverse section from each was mounted on glass and ultramilled (100μm). 50X circular polarized light images were obtained in octants and predominant CFO was expressed as the mean gray-level of each image [8]. Population densities of complete secondary osteons and their morphotype scores were also quantified [9]. Osteon morphotypes are based on collagen lamellar patterns that correlate with regional differences in habitual strain mode (compression vs. tension) [9]. The regions quantified were defined as the superior cortex (posterior, posterior-superior, superior; combined data) and inferior cortex (anterior, anterior-inferior, inferior; combined data). The rationale for these groups is based on data showing the posterior-superior to anterior-inferior axis is where fracture resistance is most compromised in the elderly [1]. Pearson correlations and one-way ANOVAs were used.

Results: CFO significantly differed between the superior and inferior cortices of the younger (<60 yrs) but not older (>60 yrs) bones (see Table). The superior vs. inferior difference is even more greatly reduced after 70yrs. By contrast, superior/inferior osteon morphotype scores and densities did not change significantly with age.

Discussion: We predicted that an age-related change in FN load history would be characterized by the emergence of prevalent/predominant tension in the superior cortex. Consequently, the previously compression-loaded superior cortex would, in theory, experience sufficient tension to evoke regional strain-mode-specific CFO adaptation. Although the results do not support this hypothesis, reduced differences in CFO between the superior and inferior cortices were found. This supports the probability that the strain environments of the superior and inferior cortices become more similar with age. This suggests a change in habitual load history as depicted in "B" of the figure, supporting the idea that underloading of the superior FN becomes prevalent with age [1]. The fact that material changes are

occurring in addition to structural changes (e.g., enlargement of FN diameter) is important because it leads to the proposal that enhancing only the natural age-related subperiosteal bone apposition that occurs in the FN would not be sufficient to curb fracture risk. This seems especially true when considering the idea that FN fractures are likely a two-stage process: the 1st stage is microdamage accumulation in the superior cortex which has deficient toughness in addition to being thinned (no fall has occurred), and the 2nd stage is the compression overloading of this region during a fall ("D" in figure). We suggest that FN bending resistance is regulated by material and structural adjustments so as to remain in equilibrium; this does not appear to be maintained with advanced age.

Significance: Knowledge of regional variations in CFO helps to advance understanding of the specific characteristics of normal bone matrix organization that degrade with age and disease (e.g. osteoporosis) in the fracture-prone FN and how these material characteristics interact with structural characteristics (e.g., cortical thickness and diameter).

References: [1] Mayhew et al. Lancet 366:129-; [2] Holzer et al. 2009 Bone 24:468-; [3] Bell et al. Bone 1999; 24:57-; [4] Loveridge et al. Bone 2004; 35: 929-; [5] Burr 2002 Bone 31:8-; [6] Kaptoge et al. 2003. Osteoporos Int 14:941-; [7] Power et al. 2005. Osteoporos Int 16(9):1049-; [8] Skedros et al. 1996 Anat Rec 246:47-; [9] Skedros et al. 2009 Bone 44:392-.

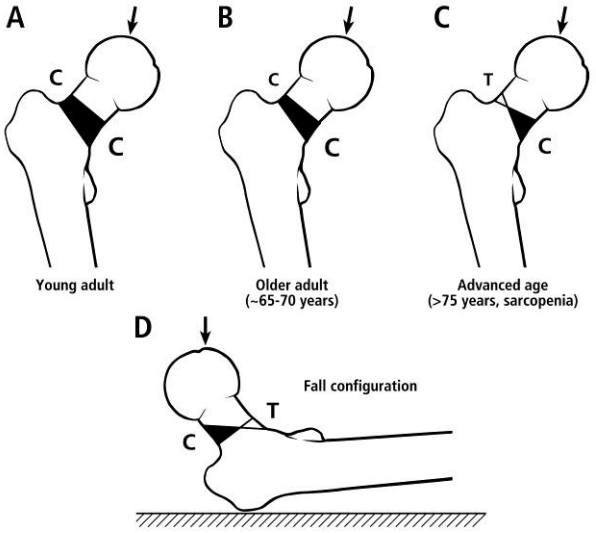
RESULTS OF CORRELATIONS (r values) & PAIRED COMPARISONS (p values)

	MTS	**OPD**	**CFO**
CORRELATIONS WITH AGE (ALL BONES; SUP/INF RATIO)	NS	NS	NS
CORRELATIONS WITH AGE (YOUNGER BONES, < 60 YEARS; SUP/INF RATIO)	NS	NS	NS
CORRELATIONS WITH AGE (OLDER BONES, ≥ 60 YEARS; SUP/INF RATIO)	NS	NS	NS
SUPERIOR vs. INFERIOR CORTEX [PAIRED COMPARISONS OF SUP vs. INF CORTICES]			
All Bones	NS	Inf > Sup *	Sup > Inf * (i.e., Sup cortex has more oblique-transverse collagen than Inf cortex)
Younger Bones (< 60 yrs.)	NS	Inf > Sup *	Sup > Inf *

Older Bones (≥ 60 yrs.)	NS	Inf > Sup *	NS (p=0.3)
INTER-PARAMETER CORRELATIONS (THESE ARE OCTANT COMPARISONS; ALL BONES)			
OPD vs. MTS	r= -0.22 *		
OPD vs. CFO	r= -0.14 (p = 0.04) *		
MTS vs. CFO	r= 0.52 *		

* = statistically significant ($p \leq 0.05$); NS= not significant; MTS = osteon morphotype score; OPD = secondary osteon population density; CFO = predominant collagen fiber orientation; Sup = superior cortex (i.e. data from P, PS, S combined); Inf = inferior cortex (i.e. data from I, AI, A combined).

NOTE: the bottom three correlation analyses are based on octant-to-octant comparisons.



The hypothesized changes in loading from young (A) to elderly (C). When an aged (B) or elderly (D) person falls the habitual low-level compression (B) or tension (C) typically experienced by the superior femoral neck is then overloaded in high compression stress. These age-related low-level strains contribute to thinning of the femoral neck. RESULTS OF THIS STUDY SUGGEST THAT THE AGE-RELATED LOADING CHANGE SUGGESTED IN "B" MIGHT OCCUR, BUT NOT THAT SHOW IN "C".

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