Hylonome

Clusters and composites:
Bone turnover and femoral neck fragility

N. Loveridge

MRC Bone Research Group, University of Cambridge Clinical School, Cambridge, UK

Introduction

Osteoporotic hip fractures are a major source of morbidity and mortality[1] and hip fracture is the most serious manifestation of osteoporosis[2]. It is predicted that the number of hip fractures will increase markedly over the next 35 years[3] and there is therefore an urgent need to develop preventative intervention strategies. Despite this, very few studies have attempted to analyse the changes in bone structure and turnover within the proximal femur. There exists a common misconception that changes in bone turnover in the ilium are in some way representative of those at the femoral neck. However, evidence from both histomorphometric and metabolic studies show that this is clearly not the case. In order to address this issue, over the past few years our group has initiated a series of case-control studies into the aetiology of femoral neck fractures with regard to the structural, histomorphometric and cellular biochemical changes associated with femoral neck fragility. These studies have led to new concepts regarding bone remodelling in general, to testable hypotheses regarding the causes of femoral neck fragility and opened up the possibility for better detection of those at risk of hip fracture.

Bone mass and fragility

The fragility of any individual bone is dependent on changes in its material properties and its distribution as well as the amount of bone tissue it contains. Age-related increases in hip fracture risk are related to the simultaneous

decreases in bone mass. However, the risk of hip fracture increases 14-fold between the ages of 60-80 but decreases in BMD only account for a 2-fold increase in risk[4]. Although the increased incidence of falls accounts for a further 1.1-1.5-fold increase in risk[4,5] this still leaves a 4-fold increase in risk which is probably related to changes in the structural and perhaps the material properties of the remaining bone[6]. The importance of these last two factors is highlighted by the studies using alendronate (an anti-resorptive bisphosphonate) in patients with low bone mass. While bone mass was increased by similar amounts in subjects with low or very low bone density, protection against hip fracture was only afforded to those with severe osteopenia prior to the start of therapeutic intervention[7]. There was little or no reduction in hip fracture rates in those subjects with mild to moderate osteopenia despite a similar increase in bone mass. An alternative explanation is that there may be underlying structural changes which are masked by such volume averaged measurements as BMD. Recent studies by Beck assessing hip strength from DXA scans seem to provide support for this concept as although bone mass declines with age hip strength does so at a much reduced rate[8-10].

Cortical or cancellous bone?

The traditional view of osteoporosis and associated fractures is that it is primarily a disease of cancellous bone. While it may be true that alterations in bone mass are most evident in trabecular bone or at predominantly trabecular sites, much of the strength of whole bones resides in the cortex. This is particularly the case in long bones such as the femur and it has been argued that extremity fractures including those of the femoral neck originate in cortical bone rather than the spongiosa[11]. This shift in emphasis is supported by both experimental evidence[12] and finite element analysis[13] indicating that the femoral neck cortex supports at least 50% of the load borne by the proximal femur. During normal gait, peak compressive stresses occur in the inferior neck cortex. These change during a sideways fall onto the greater trochanter; and peak compressive and tensile stress-
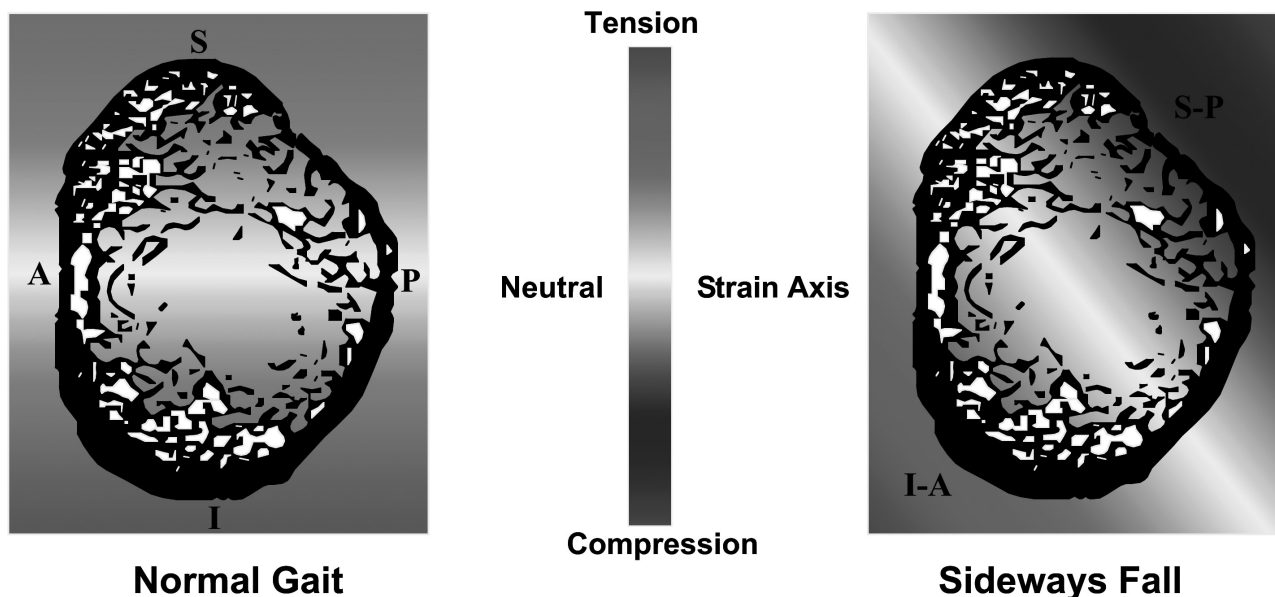
Figure 1. Schematic representation of the results of finite element models depicting the loads placed on the femoral neck during either normal gait or a sideways fall. Lotz et al.[13].

es at impact occur in the supero-posterior and infero-anterior cortex, respectively[13-15] (Figure 1). Bone that is habitually loaded in compression (such as the infero-anterior cortex) is only half as strong when it is loaded in tension[16,17] suggesting that any specific loss of cortical bone in such regions is a plausible mechanism to explain the disproportionate rise in the risk of hip fracture with ageing.

Cortical widths, porosity and remodelling

Histomorphometric and pQCT analysis of whole cross-sections of the femoral neck taken from cases of intracapsular fractures have clearly demonstrated a marked reduction in cortical bone compared to age- and gender-matched post-mortem controls, but no reduction in the amount of cancellous bone[18,19]. This reduction consisted of both decreased cortical width[18,19] and increased cortical porosity[20]. Interestingly, these changes were regionally dependent with the most affected cortices being the anterior, infero-anterior and infero-anterior regions, while the supero-posterior cortex is the thinnest in both cases and controls.

Analysis of cortical pore density and their size revealed that cases of hip fracture had an approximate doubling of the density of so called "giant" pores. These represented only the top 0.5% of the size distribution of the minimum diameter (>385µm) of pores in the control biopsies (Figure 2). Thus, the increased porosity was not related to increased formation of new Haversian systems nor to a generalised failure in remodelling balance but rather the formation of large pores in a manner representative of the changes seen in studies on disuse[21].

Analysis of cortical remodelling demonstrated marked regional variation with the anterior region of the cases of hip fracture having significant elevations in the proportion of both forming and resorbing canals. However, a mathematical model[22] of the effects of remodelling suggested that, in order to generate sufficient giant canals, anything from 35 to 15 years' worth of extra remodelling must have occurred by the time of hip fracture suggesting that some other mechanism must be involved in the formation of the giant canals.

Clusters and composites

Re-examination of the data on cortical remodelling clearly demonstrated that (on the basis of those canals undergoing formation) remodelling in the femoral neck was not randomly distributed within the cortex but was in fact clustered[22].

Approximately 60% of canals with an osteoid seam were within 375µm of another canal with an osteoid seam (Figure 3). Further studies have demonstrated that this clustering occurs at other cortical sites such as the femoral shaft[23] and the ilium. Further studies on the process of clustering would suggest that it is not age- or gender-dependent[23] and estrogen does not seem to alter the degree of clustering. Pilot data suggest the possibility that underloading of bone may play a role in the formation of remodelling clusters but this requires more extensive investigation. If remodelling osteons are clustered, then the question arises as to the mechanisms by which such systems are linked. It could be that the canals are physically separate and their activities controlled by the local release of paracrine or even neuro-
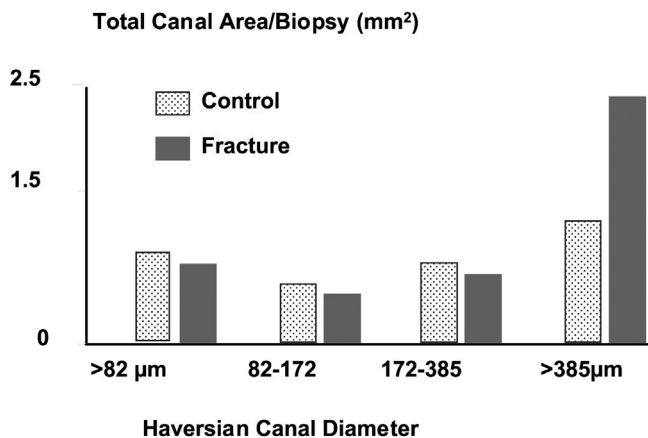
Total Canal Area/Biopsy (mm²)

Figure 2. Distribution of canal diameters in the anterior region of the femoral neck of cases of hip fracture and post mortem controls Bell et al.[20].

Figure 3. Example of a cluster of canals undergoing bone formation as evidenced by the presence of osteoid (arrows).

Figure 4. Example of a composite osteon seen in the femoral neck cortex.

logical factors with communication through osteocyte cannaliculi which have been shown to cross through the cement line from one system to another[24]. The alternative and probably more likely explanation is that the clusters are related to the physical branching of Haversian system first identified by Cohen[25] and by Tappen[26,27]. We are currently investing this possibility with µQCT and histomorphometry.

The morphology of the giant canals seen in the femoral neck (e.g., Figure 4) suggests that they could be the result of the merging of clusters during the resorption phase of BMU remodelling. Further analysis of the giant canals suggests that over 80% of them have more than one cement line strengthening the idea that some form of failure to limit bone resorption results in the merging of individual canals to form "composite" canals. Immunocytochemical studies on the expression of eNOS in osteocytes indicates that fracture cases have about a 50% reduction in osteocytes expressing eNOS and that in both cases eNOS is seen towards the periphery of individual osteons[28]. As NO is considered to be inhibitory to osteoclastic resorption[29-31] this could imply that the failure to express eNOS results in excessive bone resorption leading to the merging of individual canals to form a composite osteon.

Conclusions

Whatever the cause of the clustering, studies on the formation phase of the BMU cycle clearly demonstrate that an increased number of composite canals is deleterious to the overall bone mass. Wall widths in composite canals are about half that seen in normal osteons[32] and equivalent to those seen in the endocortical region. This raises the possibility that the relationships between clusters and composites could be part of the natural mechanisms associated with the enlargement of the medullary space as part of the natural
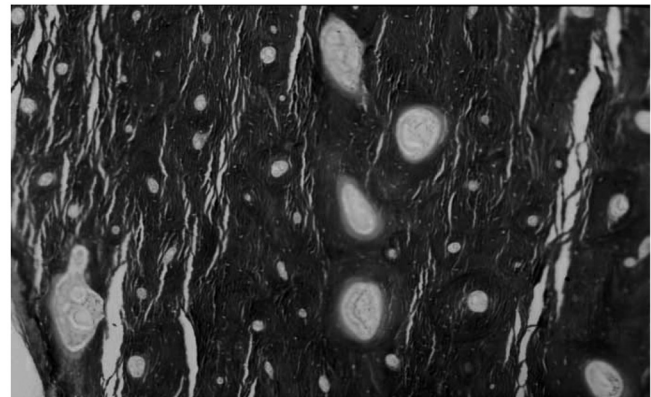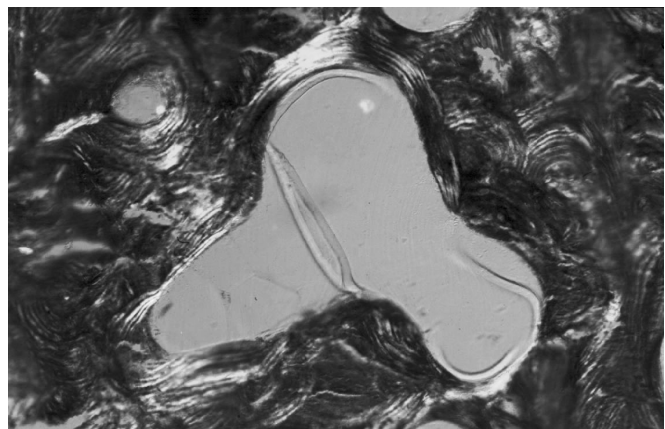
progression of ageing.

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