4. Treatment in Chronic Kidney Disease-Mineral and Bone Disorder

4a: Overview of Bone Microstructure, and Treatment of Bone Fragility in Chronic Kidney Disease.

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Chronic Kidney Disease and bone: Compromised material composition and microstructure

Bone densitometry lacks sensitivity in identifying persons sustaining fractures because most fractures occur in persons without osteoporosis.[1] Identifying these at-risk individuals is an unmet need that can, in part, be addressed by the study of bone's material composition and microstructure.[2,3] This is now possible using new low radiation CT imaging methods but few studies have been done at this time.

Bone is type 1 collagen impregnated with crystals of calcium hydroxyapatite.[4] The collagen confers flexibility enabling energy absorption by deformation. The mineral confers rigidity for loading. If under-mineralised bone (osteomalacia) deforms excessively it may fail. If homogeneously and fully mineralised bone becomes brittle it may fail. The non-collagenous helical proteins (e.g., osteopontin, osteocalcin) participate in collagen-mineral interaction providing 'hidden length' by unfolding, which minimises stress on hydroxyapatite crystals during loading.[5] Accumulation of advanced glycation end products (eg. pentosidine) during ageing, renal disease and antiresorptive therapy may compromise bone's 'toughness' -its ability to absorb energy - predisposing to fractures.[6]

Negative remodelling balance and increased remodelling rate (exacerbated by secondary hyperparathyroidism) compromise microstructure.[4] Unbalanced remodelling upon the intracortical surface of Haversian canals enlarge the canals causing cortical porosity, the source of 70% of all appendicular bone loss (because 80% of the skeleton is cortical bone).[7]

High porosity is a consistent finding in chronic kidney disease (CKD), a consistent observation in animal models of renal disease, and is the likely explanation of the high predictive value of cortical volumetric BMD for fracture (this is not found for trabecular bone or BMD).[8] Stiffness is a 7th power function of porosity so a small increase in porosity with modest bone loss disproportionately reduces stiffness.[9] Porosity is likely to be an important predictor of fracture and a target for therapy. Unbalanced trabecular remodelling erodes trabeculae yet high trabecular density is reported in some animal models of CKD. The reasons for this are obscure. One possibility is measurement errors in segmenting cortical from trabecular bone using thresholding. High intracortical remodelling produces intracortical porosity and cortical fragments which look like trabeculae. The imaging algorithm may incorrectly apportion the cortical fragments to what seems to be an enlarged

medullary canal leading to an over estimate of 'trabecular' density and an underestimate of cortical porosity.[7]

The challenge of treatment – the dearth of evidence

There are no randomised double-blind placebo-controlled trials of patients with CKD, patients on dialysis or patients after transplantation that demonstrate the antifracture efficacy of any drug. Therefore, the use of therapy is by default based on observations made in clinical trials involving persons without severe renal impairment. Most of these trials have been done in postmenopausal women with osteoporosis.[10]

Studies done using antiresorptive agents, such as the bisphosphonates alendronate, risedronate and zoledronic acid, andthe RANKL inhibitor, denosumab, confirm a consistent and robust reduction in risk of about 50-60% for vertebral fractures. All of these also demonstrate a reduction in hip fracture risk of about 50% but the reduction in nonvertebral fractures is modest, only about 20%.[10] Only risedronate, denosumab, and zoledronate have been shown to reduce the risk of all three classes of fracture - vertebral, non-vertebral and hip, by intention to treat. Alendronate reduced non-vertebral fracture risk but this was demonstrated only in a *post hoc* analysis. Drugs that have been reported to be associated with lower fracture rates in clinical trials after stratification by different levels of renal impairment include alendronate, denosumab, and risedronate,

Whether these agents reduce fracture risk in patients with severe degrees of renal impairment is not known and it is appropriate to remain sceptical until evidence is provided demonstrating antifracture efficacy in this group. The reason for this is that antiresorptive agents have several limitations*;*

First, these drugs do not abolish remodelling. Residual remodelling despite compliance with therapy is likely to erode the skeleton because the negative remodelling balance (i.e. the greater resorption of a volume of bone by each remodelling unit than is subsequently replaced) is not corrected by antiresorptive agents.[11]

Second, the suppressed remodelling rate slows structural deterioration and does slow microstructural deterioration, but it does not stop it. The microstructural deterioration present at the start of therapy is not reversed. This requires anabolic therapy. While microstructural deterioration is slowed, this comes at a price. Material composition may be compromised as the unremodelled bone becomes more completely mineralised and may accumulate advanced glycation end products leading to a more brittle material that may accumulate microcracks which are not removed in the face of reduced remodelling.[5]

Third, bisphosphonates with high mineral binding affinity like alendronate and zoledronate may not be widely distributed within thick cortical bone and so intracortical remodelling may not be prevented.[12] Denosumab does penetrate bone matrix and suppresses remodelling more than any bisphosphonate. It has been shown to reduce porosity more than alendronate but an issue of concern in renal disease is the potential for acute hypocalcemia that can be life threatening.[13]

Benefits of calcium supplementation on reduction in porosity are documented,[11] perhaps due to suppression of PTH. Vitamin D metabolites have not been convincingly shown to reduce fracture risk but calcitriol does reduce PTH levels.

There is a need for anabolic therapy in the treatment of bone fragility in patients with or without renal disease, because the antiresorptive agents do not restore the deteriorated structure of bone present at the time of diagnosis. It is unlikely PTH will be a useful anabolic agent in renal disease given the prevailing secondary hyperparathyroidism. The only other anabolic therapy being tested is an antisclerostin antibody, which has now been shown to reduce the risk of vertebral fractures within a year of starting therapy.[14]

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