How do bisphosphonates prevent fractures?

Why do fractures occur in osteoporosis?

In osteoporosis, changed bone remodelling causes loss of bone tissue and a deterioration in skeletal microstructure, which leads to an increase in skeletal fragility and risk of fracture.¹ These microstructural changes largely consist of a deterioration in skeletal microarchitecture, which affects both trabecular and cortical bone.^{2,3} In particular, the high bone turnover frequently seen in osteoporosis can produce the following changes: thinning, perforation, and complete removal of trabeculae; expansion of the medullary cavity, thereby reducing cortical thickness; an excess of partially completed cortical bone remodelling units, so increasing the proportion of cortical bone consisting of Haversian canals—that is, cortical porosity.

Recent evidence also suggests that changes in the material composition of bone may also contribute to the increase in skeletal fragility seen in osteoporosis. For example, accumulation of fatigue damage within bone, and a reduction in collagen crosslink concentration, have both been suggested to increase skeletal fragility.^{4,5} Several other independent determinants of fracture risk have also been identified, such as overall size and shape of the skeleton,^{6,7} and factors related to the risk of falling such as postural instability.⁸ However, unlike skeletal microstructure, these other factors are not thought to be influenced either by bone remodelling, or by therapeutic agents like bisphosphonates.

Summary of effects of bisphosphonates on bone

Bisphosphonates have been used to treat patients with osteoporosis since the 1980s. They are similar in structure to inorganic pyrophosphate, and bind avidly to bone where they act to inhibit osteoclast activity,⁹ although the precise mechanisms responsible for this action remain to be elucidated. Studies involving biochemical markers of bone turnover in humans have confirmed that bisphosphonates are potent suppressors of bone resorption.¹⁰ As a consequence of this action, bisphosphonates are effective at preventing further bone loss, and can even lead to substantial increases in bone mass.¹¹

These actions of bisphosphonates on bone turnover and bone mass are also associated with a beneficial effect on fracture rate. For example, cyclical administration of etidronate for two to three years has been suggested to reduce the incidence of vertebral fractures in patients with established osteoporosis by about 50%.^{12,13} Two considerably larger studies, which examined the effect of the amino-bisphosphonate alendronate have since confirmed that these agents considerably reduce the incidence of vertebral fractures.^{14,15} Furthermore, a similar protective effect was observed on the occurrence of fractures at the hip and distal radius.¹⁴

As bisphosphonates reduce fracture risk, these agents are presumably capable of improving skeletal microstructure. However, while this beneficial effect of bisphosphonates on structure is assumed to be related to their action on bone mass and bone turnover, these latter two parameters only reflect skeletal microstructure indirectly, suggesting the need for a more complete explanation as to how bisphosphonates prevent fractures. In fact, the effects of bisphosphonates and other anti-resorptive treatments on bone mass can be misleading when it comes to predicting their actions on microstructure and fracture risk. For example, after further analysis of the study by Black *et al*,¹⁴ it was suggested that the protective action of alendronate on vertebral fractures far

exceeds that predicted by changes in bone mass alone.¹⁶ This conclusion also applied to the beneficial effect of other classes of anti-resorptive agent on fracture incidence, such as hormone replacement therapy (HRT) and calcitonin. Therefore, to explain how agents like bisphosphonates prevent fractures, it is necessary to study how they influence microstructure using a more direct approach.

Possible effects of bisphosphonates on trabecular microarchitecture

Several investigators have used histomorphometric analysis of iliac crest bone biopsy specimens to study the effects of bisphosphonates on trabecular architecture.¹¹ Taken together, these results suggest that bisphosphonates act to suppress the activation of new sites of bone remodelling, and to reduce the depth of osteoclastic resorption cavities. However, while these effects might be expected to limit any subsequent deterioration in skeletal microstructure by reducing the likelihood of further trabecular perforations,¹⁷ they do not explain how skeletal microstructure could be improved, and the risk of future fractures actually decreased.

As the major changes in trabecular architecture described in osteoporosis are thought to be largely irreversible, such as loss of trabeculae,² it may be that bisphosphonates exert their beneficial influence on skeletal microstructure through other means. However, even if anti-resorptive agents cannot restore a weakened trabecular architecture, they may be able to significantly reduce skeletal fragility by strengthening those trabecular elements that remain. Consistent with this possibility, a recent histomorphometry study suggests that alendronate is able to 'un-couple' bone formation from bone resorption, because bone resorption after treatment with alendronate for two years was found to be reduced, but mean wall thickness (that is, the amount of bone laid down by individual teams of osteoblasts) to be increased.¹⁸ However, while this action might be expected to lead to trabecular thickening, whether this accounts for the decrease in skeletal fragility that follows is unclear.

In fact, although previous research has focused on changes in trabecular architecture that occur in patients with osteoporosis, it is not certain whether these are actually responsible for the increased skeletal fragility seen in this condition. For example, in another study, the degree of deterioration in trabecular architecture, as assessed on iliac crest bone biopsy specimens, was not found to predict the occurrence of fragility fractures in patients with osteoporosis.¹⁹ While there is some *in vitro* evidence to suggest that trabecular architecture contributes to compressive strength of vertebrae, the relevance of these findings to clinical fractures is unclear because in many of these studies, the cortical shell was removed before loading.²⁰

Possible effects of bisphosphonates on cortical microarchitecture

Cortical bone is also known to contribute a major part to skeletal strength, even at sites like the spine that are rich in trabecular bone.³ Thus, it is possible that structural changes in cortical rather than trabecular bone are the major cause of increased skeletal fragility in osteoporosis, and the principal targets for therapeutic agents like bisphosphonates. That cortical bone architecture is a major determinant of skeletal strength seems intuitively

correct, in view of the fact that mechanical strains are known to be greatest at the periphery of supporting structures.

There is also evidence from clinical studies that suggests that changes in cortical structure contribute significantly to the increase in skeletal fragility associated with osteoporosis. For example, in a study of patients sustaining hip fractures, femoral neck cortical porosity and thickness were found to be respectively increased and decreased in these patients.²¹ In addition, osteoporosis has recently been reported to be associated with thinning of the vertebral cortical shell, as assessed histologically.²² Furthermore, in vitro studies have found that cortical thickness and porosity contribute major parts to vertebral compressive strength and femoral neck torsional strength respectively.^{23,24}

As any tendency for cortical porosity to be increased in patients with osteoporosis probably reflects the high bone turnover that frequently occurs in this condition, this may be potentially reversible after treatment with anti-resorptive agents, in contrast with changes in trabecular microarchitecture. Unfortunately, there have been comparatively few clinical studies of the effects of anti-resorptive agents on cortical, compared with trabecular, architecture. In one recent study, however, treatment with HRT was found to significantly reduce cortical porosity, as assessed by analysis of sequential iliac crest bone biopsy specimens.²⁵ Thus, if cortical porosity is a major determinant of skeletal fragility, an improvement in this component might explain how anti-resorptive agents such as bisphosphonates are able to prevent fractures in patients with established osteoporosis.

Possible effects of bisphosphonates on bone composition

Although etidronate can impair skeletal mineralisation, this effect has not been reported after treatment with other bisphosphonates, or when etidronate is given intermittently.^{12,13} However, these agents are likely to cause other changes as a consequence of reduced bone turnover leading to an increase in bone age, although the overall impact of these on bone strength is unclear. On the one hand, the comparatively poor degree of bone mineralisation at sites undergoing rapid turnover might be expected to improve; on the other hand, excessive suppression of bone remodelling could theoretically lead to the accumulation of fatigue damage. It is also possible that bisphosphonates change the skeletal composition of collagen, following a recent report that neridronate changes the ratio of collagen crosslink fractions excreted in urine.²⁶ However, recently described effects of bisphosphonates on renal collagen crosslink handling²⁷ offer an alternative explanation for these findings.

Conclusion

It seems clear that resorption inhibitors like bisphosphonates are effective at reducing the risk of further fractures in states of established osteoporosis, suggesting that certain aspects of microstructural deterioration associated with osteoporosis are partially reversible. While it seems probable, however, that these microstructural changes involve improvements in certain aspects of skeletal microarchitecture, as yet, these remain unidentified.

Hence, despite the widespread use of anti-resorptive agents in the treatment of osteoporosis, we are still some way from understanding exactly how these drugs prevent fractures.

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